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L4 ANSWER 1 OF 7 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
2004287161 EMBASE Recent developments in the pharmacologic approach to pediatric critical care. Zuppa A.F.; Nadkarni V.M.. Dr. A.F. Zuppa, Division of Critical Care Medicine, Children's Hospital of Philadelphia, 34th and Civic Center Blvd, Philadelphia, PA 19104, United States. zuppa@email.chop.edu. Current Opinion in Anaesthesiology Vol. 17, No. 3, pp. 223-228 2004.
Refs: 62.
ISSN: 0952-7907. CODEN: COAEE2
Pub. Country: United Kingdom. Language: English. Summary Language: English.
ED Entered STN: 20040805
AB Purpose of review: There is new information supporting a resurgence of targeted use of older medications. These therapies include hydrocortisone

and vasopressin. In addition to these older drugs, newer drugs, drotrecogin α (activated protein C) and activated factor VII concentrate (NovoSeven), have been used and may improve outcome in the **treatment** of critically ill patients. This review summarizes the recent experience of these agents in the adult and pediatric critically ill populations. Recent findings: Preliminary findings are encouraging in selected septic children and adults for human recombinant activated protein C and protein C concentrate. Plasma **vasopressin levels** in pediatric septic shock and their importance have not yet been adequately studied. Recent evidence supports physiologic replacement of corticosteroids in specific adult populations. Further investigations are warranted to establish the role of activated factor VIIa in the **treatment** of critically ill children. Summary: The limited experience of protein C manipulation in critically ill septic pediatric patients makes it difficult to define its role in their care. Although it has been associated with improved outcomes, its risk profile warrants judicious use. Further prospective pediatric clinical trials are needed to define the role of vasopressin in the **treatment** of pediatric shock and cardiac arrest. The role of corticosteroids in the **treatment** of septic shock in adults and children continues to be debated. Activated factor VIIa administration to adult and pediatric patients without primary bleeding disorders has been **increasing.** Further investigations are warranted to establish the role of activated factor VIIa in the **treatment** of critically ill children.
.COPYRGT. 2004 Lippincott Williams & Wilkins.

L4 ANSWER 2 OF 7 MEDLINE on STN DUPLICATE 1

2004151335. PubMed ID: 15045037. New additions to the intensive care armamentarium. Rice Todd W; Bernard Gordon R. (Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Center for Lung Research, Nashville, Tennessee 37232-2650, USA.. todd.rice@vanderbilt.edu) . Drugs of today (Barcelona, Spain : 1998), (2004 Feb) 40 (2) 157-70. Ref: 107. Journal code: 101160518. ISSN: 0025-7656. Pub. country: Spain. Language: English.

AB Many advances have improved the care of critically ill patients, but only a few have been through the use of pharmaceutical agents. Recently, the US Food and Drug Administration (FDA) approved drotrecogin alfa (activated), or recombinant human activated protein C, for the **treatment** of patients with a high risk of death from severe sepsis. Drotrecogin alfa (activated) has antiinflammatory, antithrombotic and fibrinolytic properties. When given as a continuous intravenous infusion, recombinant human activated protein C decreases absolute mortality of severely septic patients by 6.1%, resulting in a 19.4% relative reduction in mortality. The absolute reduction in mortality increases to 13% if the population treated is restricted to patients with an APACHE II score greater than 24, as suggested by the FDA. The most frequent and serious side effect is bleeding. Severe bleeds increased from 2% in patients given placebo to 3.5% in patients receiving drotrecogin alfa (activated). The risk of bleeding was only increased during the actual infusion time of the drug, and the bleeding risk returned to placebo levels 24 hours after the infusion was discontinued. Patients treated in the intensive care unit frequently develop anemia, usually severe enough to require at least one transfusion of red blood cells. With the recent discovery of the harmful effects of allogeneic red blood cell transfusions and the **increasing** shortage of available red blood cell products, emphasis has been placed on minimizing transfusions. Patients who receive exogenous recombinant human erythropoietin maintain higher hemoglobin levels, in spite of requiring fewer transfusions during their stay in the intensive care unit. Recombinant human erythropoietin appears to be effective whether it is given as 300 units/kg of body weight subcutaneously every other day or as 40,000 units subcutaneously every week. Differences in hemoglobin values were not apparent until at least one week of therapy, but they continued to diverge after that initial week. Furthermore, the incidence of adverse events was similar to that of patients receiving placebo and there was no

difference in mortality, suggesting that avoidance of blood transfusions did not translate into increased survival. Thus, recombinant human erythropoietin appears to be both safe and effective in treating the anemia found in critically ill patients, but it is less clear that such **treatment** is cost effective, especially in the higher dose regimens. Hypotension in patients with septic shock is often difficult to correct. Despite enormous dosages of catecholamines, many of these patients continue to have inadequate blood pressures. Inadequate levels of vasopressin have been identified in patients with septic shock, as well as in other patients with hypotension secondary to refractory vasodilatation. Vasopressin is a peptide hormone secreted from the posterior pituitary in response to hyperosmolality, hypovolemia or hypotension. Levels of vasopressin initially rise in patients with septic shock, but as hypotension persists, **vasopressin levels** fall below normal. Administration of exogenous vasopressin in physiologic dosages significantly increases blood pressure in patients with shock associated with sepsis and other vasodilatory states. This rise in blood pressure is often significant enough that endogenous catecholamines can be decreased and frequently discontinued entirely. Early withdrawal of the vasopressin replacement infusion results in recurrent hypotension. Unfortunately, randomized, blinded, placebo-controlled trials showing improvement in long-term outcomes such as mortality and length of stay are still lacking.

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L4 ANSWER 3 OF 7 MEDLINE on STN DUPLICATE 2

2003538618. PubMed ID: 14619984. Smoking and the pathogenesis of gastroduodenal ulcer--recent mechanistic update. Maity Pallab; Biswas Kaushik; Roy Somenath; Banerjee Ranajit K; Bandyopadhyay Uday. (Department of Physiology, Indian Institute of Chemical Biology, Kolkata, India.) Molecular and cellular biochemistry, (2003 Nov) 253 (1-2) 329-38. Ref: 110. Journal code: 0364456. ISSN: 0300-8177. Pub. country: Netherlands. Language: English.

AB Peptic ulcer is a common disorder of gastrointestinal system and its pathogenesis is multifactorial, where smoking and nicotine have significant adverse effects. Smoking and chronic nicotine **treatment** stimulate basal acid output which is more pronounced in the smokers having duodenal ulcer. This increased gastric acid secretion is mediated through the stimulation of H2-receptor by histamine released after mast cell degranulation and due to the increase of the functional parietal cell volume or secretory capacity in smokers. Smoking and nicotine stimulate pepsinogen secretion also by **increasing** chief cell number or with an enhancement of their secretory capacity. Long-term nicotine **treatment** in rats also significantly decreases total mucus neck cell population and neck-cell mucus volume. Smoking also increases bile salt reflux rate and gastric bile salt concentration thereby **increasing** duodenogastric reflux that raises the risk of gastric ulcer in smokers. Smoking and nicotine not only induce ulceration, but they also potentiate ulceration caused by H. pylori, alcohol, nonsteroidal anti-inflammatory drugs or cold restrain stress. Polymorphonuclear neutrophils (PMN) play an important role in ulcerogenesis through oxidative damage of the mucosa by **increasing** the generation of reactive oxygen intermediates (ROI), which is potentiated by nicotine and smoking. Nicotine by a cAMP-protein kinase A signaling system elevates the endogenous **vasopressin level**, which plays an aggressive role in the development of gastroduodenal lesions. Smoking increases production of platelet activating factor (PAF) and endothelin, which are potent gastric ulcerogens. Cigarette smoking and nicotine reduce the level of circulating epidermal growth factor (EGF) and decrease the secretion of EGF from the salivary gland, which are necessary for gastric mucosal cell renewal. Nicotine also decreases prostaglandin generation in the gastric mucosa of smokers, thereby making the mucosa susceptible to ulceration. ROI generation and ROI-mediated gastric mucosal cell apoptosis are also considered to be important mechanism for aggravation of ulcer by cigarette

smoke or nicotine. Both smoking and nicotine reduce angiogenesis in the gastric mucosa through inhibition of nitric oxide synthesis thereby arresting cell renewal process. Smoking or smoke extract impairs both spontaneous and drug-induced healing of ulcer. Smoke extract also inhibits gastric mucosal cell proliferation by reducing ornithine decarboxylase activity, which synthesises growth-promoting polyamines. It is concluded that gastric mucosal integrity is maintained by an interplay of some aggressive and defensive factors controlling apoptotic cell death and cell proliferation and smoking potentiates ulcer by disturbing this balance.

L4 ANSWER 4 OF 7 MEDLINE on STN

2001358100. PubMed ID: 11242610. Nephrogenic diabetes insipidus persisting 57 months after cessation of lithium carbonate therapy: report of a case and review of the literature. Guirguis A F; Taylor H C. (Division of Endocrinology, Fairview General Hospital, Cleveland Clinic Health System, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA.) Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, (2000 Jul-Aug) 6 (4) 324-8. Ref: 22. Journal code: 9607439. ISSN: 1530-891X. Pub. country: United States. Language: English.

AB OBJECTIVE: To illuminate the natural history of prolonged nephrogenic diabetes insipidus after discontinuation of lithium carbonate **treatment** and to assess the response to therapy with desmopressin acetate and triamterene-hydrochlorothiazide. METHODS: We analyzed sequential determinations of serum and urine osmolality, plasma arginine vasopressin, serum sodium, blood urea nitrogen, calcium, ionized calcium, parathyroid hormone, and 24-hour urine volume during a period of 57 months in a 67-year-old woman. RESULTS: Our patient experienced persistent polyuria in conjunction with having repeated serum osmolalities between 300 and 323 mOsm/kg and urine osmolalities between 130 and 208 mOsm/kg. Concomitant plasma arginine **vasopressin levels** were as high as 12.0 pg/mL, consistent with the diagnosis of nephrogenic diabetes insipidus. Administration of triamterene-hydrochlorothiazide reduced 24-hour urine volume and serum osmolality while **increasing** urine osmolality. Desmopressin acetate exhibited no effect. CONCLUSION: In this report, we describe the eighth documented case of persistent nephrogenic diabetes insipidus, lasting 57 months after cessation of lithium therapy, and demonstrate a palliative effect of triamterene-hydrochlorothiazide.

L4 ANSWER 5 OF 7 MEDLINE on STN DUPLICATE 3

96152292. PubMed ID: 8557897. Dissociation of coronary vascular tolerance and neurohormonal adjustments during long-term nitroglycerin therapy in patients with stable coronary artery disease. Munzel T; Heitzer T; Kurz S; Harrison D G; Luhman C; Pape L; Olschewski M; Just H. (Medizinische Klinik III, Division of Cardiology, University of Freiburg, Germany.) Journal of the American College of Cardiology, (1996 Feb) 27 (2) 297-303. Journal code: 8301365. ISSN: 0735-1097. Pub. country: United States. Language: English.

AB OBJECTIVES. We sought to examine whether long-term nitroglycerin **treatment** causes tolerance in large coronary arteries and whether the loss of vascular effects parallels neurohormonal adjustments. BACKGROUND. Nitroglycerin therapy is associated with increased plasma renin activity and aldosterone levels and a decrease in hematocrit. It is assumed that nitroglycerin tolerance results in part from these neurohormonal adjustments and intravascular volume expansion. METHODS. Three groups were studied: group I (n = 10), no prior nitroglycerin therapy; and group II (n = 10) and group III (n = 8), 24- and 72-h long-term nitroglycerin infusion (0.5 micrograms/kg body weight per min), respectively. Coronary artery dimensions were assessed using quantitative angiography. Plasma renin activity, plasma aldosterone and **vasopressin levels** and hematocrit were monitored before and during nitroglycerin infusions. RESULTS. In group I, **increasing** intravenous concentrations of nitroglycerin caused a

dose-dependent increase of the midportion of the left anterior descending coronary artery (baseline diameter 2.13 +/- 0.07 mm [mean +/- SEM], maximally by 22 +/- 2%) and left circumflex coronary artery (baseline diameter 2.08 +/- 0.07) mm, maximally by 22 +/- 3%). An intracoronary nitroglycerin bolus (0.2 mg) caused no further significant increase in diameter, indicating maximal dilation. In group II (n = 10), the baseline large coronary artery diameter under ongoing nitroglycerin was significantly larger than that in group I (left anterior descending artery 2.61 +/- 0.08 mm, left circumflex artery 2.57 +/- 0.08 mm). Additional intravenous and intracoronary nitroglycerin challenges did not cause further dilation, indicating maximally dilated vessels. At the same time, plasma renin activity, plasma aldosterone and **vasopressin levels** were significantly increased, and hematocrit significantly decreased. In group III patients, the baseline diameter of the left anterior descending artery and the left circumflex artery did not differ from that in patients without nitroglycerin pretreatment, indicating a complete loss of nitroglycerin coronary vasodilative effects. These patients showed no significant increase in circulating neurohormonal levels but a significant decrease in hematocrit. CONCLUSIONS. Within 24 h of continuous nitroglycerin **treatment**, the coronary arteries were maximally dilated despite neurohormonal adjustments and signs of intravascular volume expansion. Within 3 days of nitroglycerin infusion, tolerance developed in the absence of neurohormonal activation. The dissociation of neurohormonal adjustments and tolerance in large coronary arteries indicates that after long-term nitroglycerin **treatment**, true vascular tolerance, perhaps from an intracellular tolerance step, may have developed.

L4 ANSWER 6 OF 7 MEDLINE on STN DUPLICATE 4

95318383. PubMed ID: 7797775. Absence of vascular tolerance in conductance vessels after 48 hours of intravenous nitroglycerin in patients with coronary artery disease. Jeserich M; Munzel T; Pape L; Fischer C; Drexler H; Just H. (Medizinische Klinik III, University of Freiburg, Germany.) Journal of the American College of Cardiology, (1995 Jul) 26 (1) 50-6. Journal code: 8301365. ISSN: 0735-1097. Pub. country: United States. Language: English.

AB OBJECTIVES. We examined whether reflex neurohormonal constrictor forces attenuate the vasodilator action of nitroglycerin on large peripheral conductance vessels. BACKGROUND. Continuous nitroglycerin therapy is associated with the development of early tolerance with respect to its hemodynamic effects. It remains to be demonstrated whether vascular tolerance of large conductance vessels is an important contributory factor. METHODS. Radial artery diameter and forearm blood flow velocity were measured before and 24 and 48 h after continuous intravenous nitroglycerin infusion (0.5 microgram/kg body weight per min) in 10 patients with coronary artery disease (mean age +/- SEM 59 +/- 4 years) by using a high resolution ultrasound device. Blood flow (ml/min) was calculated from mean blood flow velocity and cross-sectional area. RESULTS. **Increasing** concentrations of nitroglycerin led to a dose-dependent increase in radial artery diameter (maximal +24 +/- 2%) and heart rate. Forearm vascular resistance and forearm blood flow were unchanged. After 24 and 48 h of **treatment**, additional nitroglycerin did not further increase radial artery diameter, indicating that the nitroglycerin-induced dilation of the radial artery was maintained and was still maximal. In addition, radial artery diameter measured before and after 48 h of nitroglycerin infusion and after withdrawal of nitroglycerin in five additional patients showed that, after withdrawal, arterial diameter returned to baseline values within 35 min. Plasma renin activity and serum aldosterone and **vasopressin levels** increased significantly at 24 and 48 h, accompanied by a decrease in hematocrit. CONCLUSIONS. Continuous intravenous administration of nitroglycerin exerts a sustained vasodilator effect for 48 h in large conductance vessels. Neurohormonal activation and compensatory intravascular volume expansion do not attenuate the vasodilator effects of nitroglycerin on peripheral conductance vessels

during the 1st 48 h of **treatment.**

L4 ANSWER 7 OF 7 MEDLINE on STN DUPLICATE 5
87247633. PubMed ID: 3036620. Comparative study of the developmental patterns of vasopressin, glucagon, angiotensin II, and alpha 1-adrenergic receptors in the liver of developing and adult hypothyroid rats. Ali M; Cantau B; Chicot D; Clos J. Molecular and cellular endocrinology, (1987 May) 51 (1-2) 115-25. Journal code: 7500844. ISSN: 0303-7207. Pub. country: Ireland. Language: English.
AB The effects of propylthiouracil (PTU) **treatment** on vasopressin, angiotensin II, glucagon and alpha 1-adrenergic receptors in both developing and adult rats were studied in liver membrane preparations by measuring the binding of the following ligands: [3H][8-lysine]vasopressin, [3H]Sar-angiotensin II, [125I]glucagon and [3H]prazosin, and in the case of glucagon, by measuring adenylate cyclase activation. Whatever the ligand used, in young as well as in adult animals, PTU **treatment** led to a similar reduction (about 50%) in the maximal number of binding sites (Bmax), without significant changes in the apparent dissociation constant (KD) of labeled hormone for its specific receptor. In normal adult animals, thyroxine **treatment**, i.e. hyperthyroidism, had an opposite effect on the Bmax (25-50% increase), without changes in the KD. In developing PTU-treated rats, the abnormalities completely disappeared after therapy with **increasing** physiological doses of thyroxine; consequently they were directly related to thyroid deficiency and not to toxic effects of PTU. Moreover, the abnormalities resulting from induced hypothyroidism were reversible. In developing and adult hypothyroid rats, neither basal, NaF-, nor Gpp(NH)p-stimulated adenylate cyclase activities were significantly affected. Glucagon-sensitive adenylate cyclase activity seemed to be slightly increased (by about 15%), without changes in the apparent activation constant (Kact). These results are considered in parallel with findings on plasmatic glucagon and **vasopressin levels**, compared with similar previous reports related to renal vasopressin receptors, and discussed with respect to unpublished observations concerning hepatic responsiveness to glycogenolytic hormones in young and adult rats with induced hypothyroidism.

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L7 ANSWER 1 OF 2 MEDLINE on STN DUPLICATE 1
2000185798. PubMed ID: 10644657. Abnormal water metabolism in mice lacking the type 1A receptor for ANG II. Oliverio M I; Delnomdedieu M; Best C F; Li P; Morris M; Callahan M F; Johnson G A; Smithies O; Coffman T M. (Department of Medicine, Duke University, and Veterans Affairs Medical Centers, Durham, NC 27710, USA.) American journal of physiology. Renal physiology, (2000 Jan) 278 (1) F75-82. Journal code: 100901990. ISSN: 0363-6127. Pub. country: United States. Language: English.
AB Mice lacking AT(1A) receptors for ANG II have a defect in urinary concentration manifested by an inability to increase urinary osmolality to levels seen in controls after thirsting. This defect results in extreme serum hypertonicity during water deprivation. In the basal state, plasma **vasopressin levels** are similar in wild-type controls and Agtr1a -/- mice. Plasma **vasopressin levels** increase normally in the AT(1A) receptor-deficient mice after 24 h of water deprivation, suggesting that the defect in urine concentration is

intrinsic to the kidney. Using magnetic resonance microscopy, we find that the absence of AT(1A) receptors is associated with a modest reduction in the distance from the kidney surface to the tip of the papilla. However, this structural abnormality seems to play little role in the urinary concentrating defect in Agtr1a -/- mice since the impairment is largely reproduced in wild-type mice by **treatment** with an AT(1)-receptor antagonist. These studies demonstrate a critical role for the AT(1A) receptor in **maintaining** inner medullary structures in the kidney and in regulating renal water excretion.

L7 ANSWER 2 OF 2 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2000071915 EMBASE Abnormal water metabolism in mice lacking the type 1A receptor for ANG II. Oliverio M.I.; Delnomdedieu M.; Best C.F.; Li P.; Morris M.; Callahan M.F.; Johnson G.A.; Smithies O.; Coffman T.M.. T.M. Coffman, Nephrology (111I), VA Medical Center, 508 Fulton St., Durham, NC 27705, United States. tcoffman@acpub.duke.edu. American Journal of Physiology - Renal Physiology Vol. 278, No. 1 47-1, pp. F75-F82 2000.
Refs: 39.
ISSN: 0363-6127. CODEN: AJPPFK
Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20000309

AB Mice lacking AT1(A) receptors for ANG II have a defect in urinary concentration manifested by an inability to increase urinary osmolality to levels seen in controls after thirsting. This defect results in extreme serum hypertonicity during water deprivation. In the basal state, plasma **vasopressin levels** are similar in wild-type controls and Agtr 1a -/- mice. Plasma **vasopressin levels** increase normally in the AT(1A) receptor-deficient mice after 24 h of water deprivation, suggesting that the defect in urine concentration is intrinsic to the kidney. Using magnetic resonance microscopy, we find that the absence of AT(1A) receptors is associated with a modest reduction in the distance from the kidney surface to the tip of the papilla. However, this structural abnormality seems to play little role in the urinary concentrating defect in Agtr 1a -/- mice since the impairment is largely reproduced in wild-type mice by **treatment** with an AT1-receptor antagonist. These studies demonstrate a critical role for the AT(1A) receptor in **maintaining** inner medullary structures in the kidney and in regulating renal water excretion.

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2004287161 EMBASE Recent developments in the pharmacologic approach to pediatric critical care. Zuppa A.F.; Nadkarni V.M.. Dr. A.F. Zuppa, Division of Critical Care Medicine, Children's Hospital of Philadelphia, 34th and Civic Center Blvd, Philadelphia, PA 19104, United States. zuppa@email.chop.edu. Current Opinion in Anaesthesiology Vol. 17, No. 3, pp. 223-228 2004.
Refs: 62.
ISSN: 0952-7907. CODEN: COAEE2
Pub. Country: United Kingdom. Language: English. Summary Language: English.

ED Entered STN: 20040805

AB Purpose of review: There is new information supporting a resurgence of targeted use of older medications. These therapies include hydrocortisone

and vasopressin. In addition to these older drugs, newer drugs, drotrecogin α (activated protein C) and activated factor VII concentrate (NovoSeven), have been used and may improve outcome in the **treatment** of critically ill patients. This review summarizes the recent experience of these agents in the adult and pediatric critically ill populations. Recent findings: Preliminary findings are encouraging in selected septic children and adults for human recombinant activated protein C and protein C concentrate. Plasma **vasopressin levels** in pediatric septic shock and their importance have not yet been adequately studied. Recent evidence supports physiologic replacement of corticosteroids in specific adult populations. Further investigations are warranted to establish the role of activated factor VIIa in the **treatment** of critically ill children. Summary: The limited experience of protein C manipulation in critically ill septic pediatric patients makes it difficult to define its role in their care. Although it has been associated with improved outcomes, its risk profile warrants judicious use. Further prospective pediatric clinical trials are needed to define the role of vasopressin in the **treatment** of pediatric shock and cardiac arrest. The role of corticosteroids in the **treatment** of septic shock in adults and children continues to be debated. Activated factor VIIa administration to adult and pediatric patients without primary bleeding disorders has been **increasing.** Further investigations are warranted to establish the role of activated factor VIIa in the **treatment** of critically ill children.
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L9 ANSWER 2 OF 7 MEDLINE on STN DUPLICATE 1

2004151335. PubMed ID: 15045037. New additions to the intensive care armamentarium. Rice Todd W; Bernard Gordon R. (Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Center for Lung Research, Nashville, Tennessee 37232-2650, USA.. todd.rice@vanderbilt.edu) . Drugs of today (Barcelona, Spain : 1998), (2004 Feb) 40 (2) 157-70. Ref: 107. Journal code: 101160518. ISSN: 0025-7656. Pub. country: Spain. Language: English.

AB Many advances have improved the care of critically ill patients, but only a few have been through the use of pharmaceutical agents. Recently, the US Food and Drug Administration (FDA) approved drotrecogin alfa (activated), or recombinant human activated protein C, for the **treatment** of patients with a high risk of death from severe sepsis. Drotrecogin alfa (activated) has antiinflammatory, antithrombotic and fibrinolytic properties. When given as a continuous intravenous infusion, recombinant human activated protein C decreases absolute mortality of severely septic patients by 6.1%, resulting in a 19.4% relative reduction in mortality. The absolute reduction in mortality increases to 13% if the population treated is restricted to patients with an APACHE II score greater than 24, as suggested by the FDA. The most frequent and serious side effect is bleeding. Severe bleeds increased from 2% in patients given placebo to 3.5% in patients receiving drotrecogin alfa (activated). The risk of bleeding was only increased during the actual infusion time of the drug, and the bleeding risk returned to placebo levels 24 hours after the infusion was discontinued. Patients treated in the intensive care unit frequently develop anemia, usually severe enough to require at least one transfusion of red blood cells. With the recent discovery of the harmful effects of allogeneic red blood cell transfusions and the **increasing** shortage of available red blood cell products, emphasis has been placed on minimizing transfusions. Patients who receive exogenous recombinant human erythropoietin maintain higher hemoglobin levels, in spite of requiring fewer transfusions during their stay in the intensive care unit. Recombinant human erythropoietin appears to be effective whether it is given as 300 units/kg of body weight subcutaneously every other day or as 40,000 units subcutaneously every week. Differences in hemoglobin values were not apparent until at least one week of therapy, but they continued to diverge after that initial week. Furthermore, the incidence of adverse events was similar to that of patients receiving placebo and there was no

difference in mortality, suggesting that avoidance of blood transfusions did not translate into increased survival. Thus, recombinant human erythropoietin appears to be both safe and effective in treating the anemia found in critically ill patients, but it is less clear that such **treatment** is cost effective, especially in the higher dose regimens. Hypotension in patients with septic shock is often difficult to correct. Despite enormous dosages of catecholamines, many of these patients continue to have inadequate blood pressures. Inadequate levels of vasopressin have been identified in patients with septic shock, as well as in other patients with hypotension secondary to refractory vasodilatation. Vasopressin is a peptide hormone secreted from the posterior pituitary in response to hyperosmolality, hypovolemia or hypotension. Levels of vasopressin initially rise in patients with septic shock, but as hypotension persists, **vasopressin levels** fall below normal. Administration of exogenous vasopressin in physiologic dosages significantly increases blood pressure in patients with shock associated with sepsis and other vasodilatory states. This rise in blood pressure is often significant enough that endogenous catecholamines can be decreased and frequently discontinued entirely. Early withdrawal of the vasopressin replacement infusion results in recurrent hypotension. Unfortunately, randomized, blinded, placebo-controlled trials showing improvement in long-term outcomes such as mortality and length of stay are still lacking.

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L9 ANSWER 3 OF 7 MEDLINE on STN DUPLICATE 2

2003538618. PubMed ID: 14619984. Smoking and the pathogenesis of gastroduodenal ulcer--recent mechanistic update. Maity Pallab; Biswas Kaushik; Roy Somenath; Banerjee Ranajit K; Bandyopadhyay Uday. (Department of Physiology, Indian Institute of Chemical Biology, Kolkata, India.) Molecular and cellular biochemistry, (2003 Nov) 253 (1-2) 329-38. Ref: 110. Journal code: 0364456. ISSN: 0300-8177. Pub. country: Netherlands. Language: English.

AB Peptic ulcer is a common disorder of gastrointestinal system and its pathogenesis is multifactorial, where smoking and nicotine have significant adverse effects. Smoking and chronic nicotine **treatment** stimulate basal acid output which is more pronounced in the smokers having duodenal ulcer. This increased gastric acid secretion is mediated through the stimulation of H2-receptor by histamine released after mast cell degranulation and due to the increase of the functional parietal cell volume or secretory capacity in smokers. Smoking and nicotine stimulate pepsinogen secretion also by **increasing** chief cell number or with an enhancement of their secretory capacity. Long-term nicotine **treatment** in rats also significantly decreases total mucus neck cell population and neck-cell mucus volume. Smoking also increases bile salt reflux rate and gastric bile salt concentration thereby **increasing** duodenogastric reflux that raises the risk of gastric ulcer in smokers. Smoking and nicotine not only induce ulceration, but they also potentiate ulceration caused by H. pylori, alcohol, nonsteroidal anti-inflammatory drugs or cold restrain stress. Polymorphonuclear neutrophils (PMN) play an important role in ulcerogenesis through oxidative damage of the mucosa by **increasing** the generation of reactive oxygen intermediates (ROI), which is potentiated by nicotine and smoking. Nicotine by a cAMP-protein kinase A signaling system elevates the endogenous **vasopressin level**, which plays an aggressive role in the development of gastroduodenal lesions. Smoking increases production of platelet activating factor (PAF) and endothelin, which are potent gastric ulcerogens. Cigarette smoking and nicotine reduce the level of circulating epidermal growth factor (EGF) and decrease the secretion of EGF from the salivary gland, which are necessary for gastric mucosal cell renewal. Nicotine also decreases prostaglandin generation in the gastric mucosa of smokers, thereby making the mucosa susceptible to ulceration. ROI generation and ROI-mediated gastric mucosal cell apoptosis are also considered to be important mechanism for aggravation of ulcer by cigarette

smoke or nicotine. Both smoking and nicotine reduce angiogenesis in the gastric mucosa through inhibition of nitric oxide synthesis thereby arresting cell renewal process. Smoking or smoke extract impairs both spontaneous and drug-induced healing of ulcer. Smoke extract also inhibits gastric mucosal cell proliferation by reducing ornithine decarboxylase activity, which synthesises growth-promoting polyamines. It is concluded that gastric mucosal integrity is maintained by an interplay of some aggressive and defensive factors controlling apoptotic cell death and cell proliferation and smoking potentiates ulcer by disturbing this balance.

L9 ANSWER 4 OF 7 MEDLINE on STN

2001358100. PubMed ID: 11242610. Nephrogenic diabetes insipidus persisting 57 months after cessation of lithium carbonate therapy: report of a case and review of the literature. Guirguis A F; Taylor H C. (Division of Endocrinology, Fairview General Hospital, Cleveland Clinic Health System, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA.) Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, (2000 Jul-Aug) 6 (4) 324-8. Ref: 22. Journal code: 9607439. ISSN: 1530-891X. Pub. country: United States. Language: English.

AB OBJECTIVE: To illuminate the natural history of prolonged nephrogenic diabetes insipidus after discontinuation of lithium carbonate **treatment** and to assess the response to therapy with desmopressin acetate and triamterene-hydrochlorothiazide. METHODS: We analyzed sequential determinations of serum and urine osmolality, plasma arginine vasopressin, serum sodium, blood urea nitrogen, calcium, ionized calcium, parathyroid hormone, and 24-hour urine volume during a period of 57 months in a 67-year-old woman. RESULTS: Our patient experienced persistent polyuria in conjunction with having repeated serum osmolalities between 300 and 323 mOsm/kg and urine osmolalities between 130 and 208 mOsm/kg. Concomitant plasma arginine **vasopressin levels** were as high as 12.0 pg/mL, consistent with the diagnosis of nephrogenic diabetes insipidus. Administration of triamterene-hydrochlorothiazide reduced 24-hour urine volume and serum osmolality while **increasing** urine osmolality. Desmopressin acetate exhibited no effect. CONCLUSION: In this report, we describe the eighth documented case of persistent nephrogenic diabetes insipidus, lasting 57 months after cessation of lithium therapy, and demonstrate a palliative effect of triamterene-hydrochlorothiazide.

L9 ANSWER 5 OF 7 MEDLINE on STN DUPLICATE 3

96152292. PubMed ID: 8557897. Dissociation of coronary vascular tolerance and neurohormonal adjustments during long-term nitroglycerin therapy in patients with stable coronary artery disease. Munzel T; Heitzer T; Kurz S; Harrison D G; Luhman C; Pape L; Olschewski M; Just H. (Medizinische Klinik III, Division of Cardiology, University of Freiburg, Germany.) Journal of the American College of Cardiology, (1996 Feb) 27 (2) 297-303. Journal code: 8301365. ISSN: 0735-1097. Pub. country: United States. Language: English.

AB OBJECTIVES. We sought to examine whether long-term nitroglycerin **treatment** causes tolerance in large coronary arteries and whether the loss of vascular effects parallels neurohormonal adjustments. BACKGROUND. Nitroglycerin therapy is associated with increased plasma renin activity and aldosterone levels and a decrease in hematocrit. It is assumed that nitroglycerin tolerance results in part from these neurohormonal adjustments and intravascular volume expansion. METHODS. Three groups were studied: group I (n = 10), no prior nitroglycerin therapy; and group II (n = 10) and group III (n = 8), 24- and 72-h long-term nitroglycerin infusion (0.5 micrograms/kg body weight per min), respectively. Coronary artery dimensions were assessed using quantitative angiography. Plasma renin activity, plasma aldosterone and **vasopressin levels** and hematocrit were monitored before and during nitroglycerin infusions. RESULTS. In group I, **increasing** intravenous concentrations of nitroglycerin caused a

dose-dependent increase of the midportion of the left anterior descending coronary artery (baseline diameter 2.13 +/- 0.07 mm [mean +/- SEM], maximally by 22 +/- 2%) and left circumflex coronary artery (baseline diameter 2.08 +/- 0.07) mm, maximally by 22 +/- 3%). An intracoronary nitroglycerin bolus (0.2 mg) caused no further significant increase in diameter, indicating maximal dilation. In group II (n = 10), the baseline large coronary artery diameter under ongoing nitroglycerin was significantly larger than that in group I (left anterior descending artery 2.61 +/- 0.08 mm, left circumflex artery 2.57 +/- 0.08 mm). Additional intravenous and intracoronary nitroglycerin challenges did not cause further dilation, indicating maximally dilated vessels. At the same time, plasma renin activity, plasma aldosterone and **vasopressin levels** were significantly increased, and hematocrit significantly decreased. In group III patients, the baseline diameter of the left anterior descending artery and the left circumflex artery did not differ from that in patients without nitroglycerin pretreatment, indicating a complete loss of nitroglycerin coronary vasodilative effects. These patients showed no significant increase in circulating neurohormonal levels but a significant decrease in hematocrit. CONCLUSIONS. Within 24 h of continuous nitroglycerin **treatment**, the coronary arteries were maximally dilated despite neurohormonal adjustments and signs of intravascular volume expansion. Within 3 days of nitroglycerin infusion, tolerance developed in the absence of neurohormonal activation. The dissociation of neurohormonal adjustments and tolerance in large coronary arteries indicates that after long-term nitroglycerin **treatment**, true vascular tolerance, perhaps from an intracellular tolerance step, may have developed.

L9 ANSWER 6 OF 7 MEDLINE on STN DUPLICATE 4

95318383. PubMed ID: 7797775. Absence of vascular tolerance in conductance vessels after 48 hours of intravenous nitroglycerin in patients with coronary artery disease. Jeserich M; Munzel T; Pape L; Fischer C; Drexler H; Just H. (Medizinische Klinik III, University of Freiburg, Germany.) Journal of the American College of Cardiology, (1995 Jul) 26 (1) 50-6. Journal code: 8301365. ISSN: 0735-1097. Pub. country: United States. Language: English.

AB OBJECTIVES. We examined whether reflex neurohormonal constrictor forces attenuate the vasodilator action of nitroglycerin on large peripheral conductance vessels. BACKGROUND. Continuous nitroglycerin therapy is associated with the development of early tolerance with respect to its hemodynamic effects. It remains to be demonstrated whether vascular tolerance of large conductance vessels is an important contributory factor. METHODS. Radial artery diameter and forearm blood flow velocity were measured before and 24 and 48 h after continuous intravenous nitroglycerin infusion (0.5 microgram/kg body weight per min) in 10 patients with coronary artery disease (mean age +/- SEM 59 +/- 4 years) by using a high resolution ultrasound device. Blood flow (ml/min) was calculated from mean blood flow velocity and cross-sectional area. RESULTS. **Increasing** concentrations of nitroglycerin led to a dose-dependent increase in radial artery diameter (maximal +24 +/- 2%) and heart rate. Forearm vascular resistance and forearm blood flow were unchanged. After 24 and 48 h of **treatment**, additional nitroglycerin did not further increase radial artery diameter, indicating that the nitroglycerin-induced dilation of the radial artery was maintained and was still maximal. In addition, radial artery diameter measured before and after 48 h of nitroglycerin infusion and after withdrawal of nitroglycerin in five additional patients showed that, after withdrawal, arterial diameter returned to baseline values within 35 min. Plasma renin activity and serum aldosterone and **vasopressin levels** increased significantly at 24 and 48 h, accompanied by a decrease in hematocrit. CONCLUSIONS. Continuous intravenous administration of nitroglycerin exerts a sustained vasodilator effect for 48 h in large conductance vessels. Neurohormonal activation and compensatory intravascular volume expansion do not attenuate the vasodilator effects of nitroglycerin on peripheral conductance vessels

during the 1st 48 h of **treatment**.

L9 ANSWER 7 OF 7 MEDLINE on STN DUPLICATE 5
87247633. PubMed ID: 3036620. Comparative study of the developmental patterns of vasopressin, glucagon, angiotensin II, and alpha 1-adrenergic receptors in the liver of developing and adult hypothyroid rats. Ali M; Cantau B; Chicot D; Clos J. Molecular and cellular endocrinology, (1987 May) 51 (1-2) 115-25. Journal code: 7500844. ISSN: 0303-7207. Pub. country: Ireland. Language: English.

AB The effects of propylthiouracil (PTU) **treatment** on vasopressin, angiotensin II, glucagon and alpha 1-adrenergic receptors in both developing and adult rats were studied in liver membrane preparations by measuring the binding of the following ligands: [3H][8-lysine]vasopressin, [3H]Sar-angiotensin II, [125I]glucagon and [3H]prazosin, and in the case of glucagon, by measuring adenylate cyclase activation. Whatever the ligand used, in young as well as in adult animals, PTU **treatment** led to a similar reduction (about 50%) in the maximal number of binding sites (Bmax), without significant changes in the apparent dissociation constant (KD) of labeled hormone for its specific receptor. In normal adult animals, thyroxine **treatment**, i.e. hyperthyroidism, had an opposite effect on the Bmax (25-50% increase), without changes in the KD. In developing PTU-treated rats, the abnormalities completely disappeared after therapy with **increasing** physiological doses of thyroxine; consequently they were directly related to thyroid deficiency and not to toxic effects of PTU. Moreover, the abnormalities resulting from induced hypothyroidism were reversible. In developing and adult hypothyroid rats, neither basal, NaF-, nor Gpp(NH)p-stimulated adenylate cyclase activities were significantly affected. Glucagon-sensitive adenylate cyclase activity seemed to be slightly increased (by about 15%), without changes in the apparent activation constant (Kact). These results are considered in parallel with findings on plasmatic glucagon and **vasopressin levels**, compared with similar previous reports related to renal vasopressin receptors, and discussed with respect to unpublished observations concerning hepatic responsiveness to glycogenolytic hormones in young and adult rats with induced hypothyroidism.

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=> s l1 and anti-PTHrP
L10          0 L1 AND ANTI-PTHRP

=> s parathyroid hormone related peptide
L11       3807 PARATHYROID HORMONE RELATED PEPTIDE

=> s l11 and vasoprressin level
L12          0 L11 AND VASOPRRESSIN LEVEL

=> s l11 and antibod?
L13        319 L11 AND ANTIBOD?

=> s l13 and monoclonal
L14         98 L13 AND MONOCLONAL

=> s l14 and FERM BP-5631
L15          0 L14 AND FERM BP-5631

=> dup remove l14
PROCESSING COMPLETED FOR L14
L16         41 DUP REMOVE L14 (57 DUPLICATES REMOVED)

=> s l16 and vasopressin
L17          0 L16 AND VASOPRESSIN

=> d l16 1-41 cbib abs
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L16 ANSWER 1 OF 41 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on

STN
2005:773004 The Genuine Article (R) Number: 947CK. PTHrP and PTH/PTHrP receptor 1 expression in odontogenic cells of normal and HHM model rat incisors. Kato A (Reprint); Suzuki M; Karasawa Y; Sugimoto T; Doi K. Chugai Pharmaceut Co Ltd, Dept Safety Assessment, 1-135 Komakado, Gotemba, Shizuoka 4128513, Japan (Reprint); Chugai Pharmaceut Co Ltd, Dept Safety Assessment, Gotemba, Shizuoka 4128513, Japan; Univ Tokyo, Fac Agr, Dept Vet Pathol, Bunkyo Ku, Tokyo 1138657, Japan. katoath@chugai-pharm.co.jp. TOXICOLOGIC PATHOLOGY (2005) Vol. 33, No. 4, pp. 456-464. ISSN: 0192-6233. Publisher: TAYLOR & FRANCIS INC, 325 CHESTNUT ST, SUITE 800, PHILADELPHIA, PA 19106 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Parathyroid hormone related peptide** (PTHrP) was discovered as a causative factor of humoral hypercalcemia of malignancy (HHM). We examined PTHrP and its receptor (PTHR1) expression patterns in odontogenic cells in normal and HHM model rat incisors. Nontreated nude rats serving as the normal control and HHM model rats produced by implantation of PTHrP-expressing tumor (LC-6) cells were prepared. HHM rats fractured its incisor, and histopathologically, restrict population of odontoblasts showed findings classified as "shortening of high columnar odontoblasts" and "dentin niche." The incisors were immunostained against PTHrP and PTHR1. In normal rats, PTHrP and PTHR1 colocalized in ameloblasts, cementoblasts, and odontoblastic cells from mesenchymal cells to columnar odontoblasts. In high columnar odontoblasts, PTHrP solely expressed. In the HHM animals, although the expression patterns were identical to those of the normal rats in normal area, the shortened high columnar odontoblasts maintained PTHR1 expression and dentin niche comprising odontoblastic cells expressed both proteins. In the HHM model, the protein expression patterns changed in the odontoblastic cells with histological anomalies, and thus direct relations between the anomalies and PTHrP/PTHR1 axis are suggested.

L16 ANSWER 2 OF 41 MEDLINE on STN DUPLICATE 1
2005175865. PubMed ID: 15809528. Systemic inflammation, cachexia and prognosis in patients with cancer. Deans Christopher; Wigmore Stephen J. (Tissue Injury and Repair Group, MRC Centre for Inflammation Research, Department of Clinical and Surgical Sciences, Medical School, Edinburgh University, Scotland, UK.) Current opinion in clinical nutrition and metabolic care, (2005 May) 8 (3) 265-9. Journal code: 9804399. ISSN: 1363-1950. Pub. country: England: United Kingdom. Language: English.

AB PURPOSE OF REVIEW: Cachexia remains an important cause of morbidity and mortality among cancer patients. The mechanisms underlying this syndrome remain unclear and are almost certainly multifactorial. Evidence from animal models suggests a compelling link between cachexia and inflammation, and a variety of pro-inflammatory cytokines play an integral role. This review summarizes current thinking relating to inflammation, cachexia and prognosis in cancer patients, with particular emphasis on studies relating to recent therapeutic advances. RECENT FINDINGS: Pro-inflammatory cytokines induce the acute phase protein response, a key marker of systemic inflammation. Recent evidence has also implicated other tumour-derived mediators, such as proteolysis-inducing factor and **parathyroid hormone-related peptide.**
In addition, systemic inflammation has been found in association with many malignancies, and has been correlated with weight loss, hypermetabolism, anorexia, and adverse prognosis. Treatments such as fish oil, **monoclonal antibodies**, and non-steroidal
anti-inflammatory drugs, have all been utilized to attenuate systemic inflammation and influence weight loss. Recent clinical studies have suggested that eicosapentaenoic acid and cyclo-oxygenase 2 inhibitors promote weight gain and downregulate the acute phase protein response. SUMMARY: Pro-inflammatory processes are clearly implicated in the hypermetabolism and weight loss associated with cancer-associated cachexia. In addition, the presence of systemic inflammation is now clearly linked with adverse prognosis in patients with cancer, which cannot be fully explained by the association with weight loss. Systemic

inflammation remains an important area for novel therapeutic targets in combating cachexia, and eicosapentaenoic acid and cyclo-oxygenase 2 inhibitors appear to be efficacious in the armory against cachexia.

L16 ANSWER 3 OF 41 CAPLUS COPYRIGHT 2005 ACS on STN
2004:453054 Document No. 141:1229 Remedy for chondroma or chondrosarcoma. Yoshikawa, Hideki; Miyaji, Takahiro (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2004045643 A1 20040603, 143 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2003-JP10627 20030822. PRIORITY: JP 2002-334081 20021118.
AB A novel remedy for chondroma or chondrosarcoma containing a substance which inhibits the binding of a **parathyroid hormone-related peptide** to its receptor for improving the prognosis of chondroma or chondrosarcoma.

L16 ANSWER 4 OF 41 CAPLUS COPYRIGHT 2005 ACS on STN
2004:162552 Document No. 140:211343 Methods for the production and uses of PTHrP C-terminal mutants in the modulation of smooth muscle cells proliferation and therapeutic uses thereof. Stewart, Andrew F.; Fiaschi-Taesch, Nathalie (Osteotrophin, LLC, USA). PCT Int. Appl. WO 2004016151 A2 20040226, 100 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US25473 20030813. PRIORITY: US 2002-2002/PV403805 20020815.
AB The present invention relates to the use of mutants of parathyroid hormone-related protein, to treat disorders associated with smooth muscle cells, and to inhibit the cellular activation and proliferation thereof. Nucleic acids encoding and **antibodies** to the proteins of the invention are addnl. claimed as are pharmaceutical compns. containing the nucleic acids, protein and **antibodies.** Also claimed are medical devices coated with the proteins of the invention, kits containing the pharmaceutical compns., and methods for screening agents that bind to the mutants. The method can be employed in diverse tissues to effect therapeutic and prophylactic relief for disorders and diseases manifested by activation of smooth muscle that can lead to excessive smooth muscle proliferation. For example, where employed in the vasculature, the inventive method can be used to treat restenosis following angioplasty.

L16 ANSWER 5 OF 41 CAPLUS COPYRIGHT 2005 ACS on STN
2003:633504 Document No. 139:178708 Role of T-cell immune response cDNA 7 (TIRC7) in phagocytosis and lymphocyte activation. Utku, Nalan (Germany). PCT Int. Appl. WO 2003066091 A2 20030814, 70 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP1083 20030204. PRIORITY: EP 2002-1980 20020204.
AB The author discloses the prevention and treatment of mammalian disorders

by modulation of effects of TIRC7 on phagocyte and lymphoid cell populations. Furthermore, improved methods for the production of Igs to a desired antigen are described. This invention is based on the discovery of a mechanism for the regulation of phagocytosis and the response of lymphoid cell populations to antigens.

L16 ANSWER 6 OF 41 CAPLUS COPYRIGHT 2005 ACS on STN
2003:282718 Document No. 138:282352 Traversal of nucleic acid molecules through a tissue fluid space and expression in repair cells. Sosnowski, Barbara A.; Pierce, Glenn (Selective Genetics, Inc., USA). PCT Int. Appl. WO 2003029429 A2 20030410, 95 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US31546 20021002. PRIORITY: US 2001-2001/PV327513 20011003.

AB Disclosed are methods for use in transferring nucleic acids into cells at a wound site associated with a fluid space. These gene transfer protocols are suitable for use in transferring various nucleic acids into cartilage, cardiac muscle, and other tissues, and have many uses including treating diseases such as arthritis and ischemic heart disease, and promoting wound healing. The invention further disclosed pharmaceutical compns. that may be used in the practice of the invention to transfer the nucleic acid of interest. Such compns. include any multi-partitioned biocompatible matrix in combination with multiple nucleic acids of interest. Thus, collagen collagen-immobilized fibroblast growth factor (FGF) genes induce angiogenesis in vitro, and FGF gene delivery to skeletal muscle wounds induces both angiogenesis and arteriogenesis and well as induces myocyte regeneration.

L16 ANSWER 7 OF 41 MEDLINE on STN DUPLICATE 2
2003132905. PubMed ID: 12647214. Prognostic value of immunocytochemical determination of **parathyroid hormone-related peptide** expression in cells of mammary ductal carcinoma. Analysis of 7 years of the disease course. Surowiak Pawel; Dziegiel Piotr; Matkowski Rafal; Sopel Miroslaw; Wojnar Andrzej; Kornafel Jan; Zabel Maciej. (Department of Histology and Embryology, University School of Medicine, ul.Chalubinskiego 6a, 50-356, Wroclaw, Poland.. pawel.surowiak@interia.pl) . Virchows Archiv : an international journal of pathology, (2003 Mar) 442 (3) 245-51. Electronic Publication: 2003-01-25. Journal code: 9423843. ISSN: 0945-6317. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB **Parathyroid hormone-related peptide** (PTHrP) participates in the development of humoral hypercalcaemia of malignancy. The peptide is thought to affect growth and differentiation of normal and neoplastic cells. The present study aimed at evaluation of the relationship between survival time and development of distant metastases in patients with ductal mammary carcinoma on the one hand and PTHrP expression on the other. Immunocytochemical reactions using mouse **monoclonal** (clone 212-10.7) anti-PTHrP (38-64) **antibodies** were performed in paraffin sections originating from 47 patients with ductal mammary carcinoma. Expression of the protein was quantified employing a scale, considering the number of positive cells and intensity of the reaction (immunoreactive score, IRS). Survival time of the patients, determined during the course of a 7-year observation was also analysed. The obtained results demonstrated a relationship between intensity of PTHrP expression and the survival time. Patients with high expression of PTHrP (IRS>6) manifested longer survival than patients with lower PTHrP expression (IRS< or =6; Cox'es F test, P<0.05). Moreover, in the group with the lower PTHrP expression, a negative relationship was detected between expression of the protein and the survival time (Cox'es

model, P<0.05). No relationship was detected between PTHrP expression and the development of distant metastases.

L16 ANSWER 8 OF 41 CAPLUS COPYRIGHT 2005 ACS on STN
2002:888597 Document No. 138:3671 Angiogenesis inhibitors that block binding of PTH-related peptide to its receptor for use as antitumor agents. Saito, Hidemi; Tsunenari, Toshiaki; Onuma, Etsuro; Kato, Atsuhiko; Suzuki, Masami (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2002092133 A1 20021121, 110 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2002-JP4586 20020510. PRIORITY: JP 2001-140659 20010510.
AB It is found out that angiogenesis can be inhibited by a substance which inhibits the binding of a parathyroid hormone-associated peptide (e.g. PTHrP) to its receptor. The angiogenesis inhibitors can be anti-PTHrP **antibodies**, **antibody** fragments, humanized or chimeric **antibodies**, PTH receptor antagonists, or antisense oligonucleotides specific to PTHrP. These modified anti-PTHrP **antibodies** and PTH receptor antagonists are useful as antitumor agents and bone metastasis inhibitors.

L16 ANSWER 9 OF 41 CAPLUS COPYRIGHT 2005 ACS on STN
2002:142554 Document No. 136:198926 **Antibodies** or inhibitors that block binding of PTH receptor or PTH-related protein receptor for ameliorating symptoms caused by joint diseases. Yoshikawa, Hideki (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2002013865 A1 20020221, 112 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2001-JP7044 20010815. PRIORITY: JP 2000-247013 20000816.
AB Agents for ameliorating symptoms caused by joint diseases relating to PTH or PTHrP. It is found out that joint diseases and symptoms caused by joint diseases can be ameliorated by a substance inhibiting the binding of a **parathyroid hormone-related peptide** to its receptor. The substances are **antibodies** or **monoclonal antibodies** specific to PTH-related protein, **antibody** fragments, and chimeric or humanized **antibodies.** The joint disease is rheumatoid arthritis, arthritis deformans, or chronic rheumatoid arthritis.

L16 ANSWER 10 OF 41 MEDLINE on STN DUPLICATE 3
2002452343. PubMed ID: 12080067. Purification and characterization of a receptor for human parathyroid hormone and **parathyroid hormone-related peptide.** Shimada Masako; Chen Xin; Cvrk Tomas; Hilfiker Helene; Parfenova Maria; Segre Gino V. (Endocrine Unit, Massachusetts General Hospital and Department of Medicine, Harvard Medical School, Boston, Massachusetts 02114, USA.) Journal of biological chemistry, (2002 Aug 30) 277 (35) 31774-80. Electronic Publication: 2002-06-21. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB The human parathyroid hormone (PTH) receptor (hPTH1R), containing a 9-amino acid sequence of rhodopsin at its C terminus, was transiently expressed in COS-7 cells and solubilized with 0.25% n-dodecyl maltoside. Approximately 18 microg of hPTH1R were purified to homogeneity per mg of

crude membranes by single-step affinity chromatography using 1D4, a **monoclonal antibody** to a rhodopsin epitope. The N terminus of the hPTH1R is Tyr(23), consistent with removal of the 22-amino acid signal peptide. Comparisons of hPTH1R by quantitative immunoblotting and Scatchard analysis revealed that 75% of the receptors in membrane preparations were functional; there was little, if any, loss of functional receptors during purification. The binding affinity of the purified hPTH1R was slightly lower than membrane-embedded hPTH1R (K(d) = 16.5 +/- 1.3 versus 11.9 +/- 1.9 nm), and the purified receptors bound rat [Nle(8,21),Tyr(34)]PTH-(1-34)-NH(2) (PTH-(1-34)), and rat [Ile(5),Trp(23),Tyr(36)]PTHrP-(5-36)-NH(2) with indistinguishable affinity. Maximal displacement of (125)I-PTH-(1-34) binding by rat [alpha-aminoisobutyric acid (Aib)(1,3),Nle(8),Gln(10),Har(11),Ala(12),Trp(14),Arg(19),Tyr(21)]PTH-(1-21)-NH(2) and rat [Aib(1,3),Gln(10),Har(11),Ala(12),Trp(14)]PTH-(1-14)-NH(2) of 80 and 10%, respectively, indicates that both N-terminal and juxtamembrane ligand binding determinants are functional in the purified hPTH1R. Finally, PTH stimulated [(35)S]GTP gamma S incorporation into G alpha(s) in a time- and dose-dependent manner, when recombinant hPTH1R, G alpha(s)-, and beta gamma-subunits were reconstituted in phospholipid vesicles. The methods described will enable structural studies of the hPTH1R, and they provide an efficient and general technique to purify proteins, particularly those of the class II G protein-coupled receptor family.

L16 ANSWER 11 OF 41 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

2003284992 EMBASE Hypercalcemia of malignancy: Pathophysiology diagnosis and treatment. Hotte S.J.; Hirte H.W.; Rabbani S.A.; Carling T.; Hendy G.N.; Major P.P.. Dr. S.J. Hotte, Hamilton Regional Cancer Centre, 699 Concession Street, Hamilton, Ont. L8V 5C2, Canada. sebastien.hotte@hrcc.on.ca. American Journal of Cancer Vol. 1, No. 3, pp. 179-187 2002.
Refs: 94.
ISSN: 1175-6357. CODEN: AJCMCB
Pub. Country: New Zealand. Language: English. Summary Language: English.

ED Entered STN: 20030731

AB Hypercalcemia of malignancy (HCM) is the most common cause of elevated serum calcium in hospitalized patients and is found with varying frequency in patients with various types of cancer. Calcium homeostasis is finely regulated with day-to-day variations of less than 2%, and the development of HCM stems from various anomalies in homeostatic mechanisms. Hypercalcemia of ten produces a number of clinical symptoms, including alterations in central nervous system function, symptoms of dehydration and renal dysfunction. Whenever possible and appropriate, the goals of treatment of HCM should therefore be to return the patient to a euvolemic state, to normalize serum calcium and to treat the underlying cause. Almost invariably, however, HCM is a particularly adverse complication for patients with cancer and is almost always associated with a dismal prognosis. Older treatments like mithramycin and calcitonin have recently been replaced with newer management strategies, mostly involving bisphosphonates. These agents are potent inhibitors of osteoclasts which have been found to normalize serum calcium levels in a high proportion of patients with HCM. Emerging therapeutic approaches include **monoclonal antibodies** to **parathyroid hormone related peptide** (PTHrP), inhibition of RANK ligand through the use of a soluble form of its receptor osteoprotegerin, analogues of Vitamin D and selective inhibiton of the Ras-Raf-MAPK-ERK signalling pathway. In this article, we review the pathophysiology of tumour osteolysis leading to hypercalcemia of malignancy, and we discuss the physiological basis for the clinical symptoms of hypercalcemia. Past, current and future therapeutic approaches are also reviewed.

L16 ANSWER 12 OF 41 MEDLINE on STN

2002461549. PubMed ID: 12220122. Expression of **parathyroid**

hormone-related peptide (PthrP) and its receptor (PTH1R) during the histogenesis of cartilage and bone in the chicken mandibular process. Zhao Qiong; Brauer Philip R; Xiao Lei; McGuire Michael H; Yee John A. (Department of Biomedical Sciences, Creighton University, School of Medicine, Omaha, NE 68178, USA.) Journal of anatomy, (2002 Aug) 201 (2) 137-51. Journal code: 0137162. ISSN: 0021-8782. Pub. country: England: United Kingdom. Language: English.

AB The purpose of this study was to examine the expression and actions of parathyroid hormone-related protein (PTHrP) when skeletal histogenesis occurs in the chicken mandible. Prior to the appearance of skeletal tissues, PTHrP and PTH1R were co-expressed by cells in the ectoderm, skeletal muscle, peripheral nerve and mesenchyme. Hyaline cartilage was first observed at HH stage 27 when many but not all chondroblasts expressed PTHrP and PTH1R. By stage 34, PTHrP and PTH1R were not detected in chondrocytes but were expressed in the perichondrium. Alkaline phosphatase (AP)-positive preosteoblasts and woven bone appeared at stages 31 and 34, respectively. Preosteoblasts, osteoblasts and osteocytes co-expressed PTHrP and PTH1R. Treatment with chicken PTHrP (1-36) increased cAMP in mesenchyme from stage 26 embryos. Continuous exposure to chicken PTHrP (1-36) for 14 days increased cartilage nodule number and decreased AP while intermittent exposure did not affect cartilage nodule number and increased AP in cultures of stage 26 mesenchymal cells. Adding a neutralizing anti-PTHrP **antibody** to the cultures reduced cartilage nodule number and did not affect AP. These findings show that PTHrP and PTH1R are co-expressed by extraskeletal and skeletal cells before and during skeletal tissue histogenesis, and that PTHrP may influence skeletal tissue histogenesis by affecting the differentiation of mandibular mesenchymal cells into chondroblasts and osteoblasts.

L16 ANSWER 13 OF 41 MEDLINE on STN DUPLICATE 4

2004293871. PubMed ID: 15195132. **Parathyroid hormone-related peptide**: expression in prostate cancer bone metastases. Bryden A A G; Islam S; Freemont A J; Shanks J H; George N J R; Clarke N W. (Christie and Hope Hospitals, Manchester, UK.. gbryden@hotmail.com) . Prostate cancer and prostatic diseases, (2002) 5 (1) 59-62. Journal code: 9815755. ISSN: 1365-7852. Pub. country: England: United Kingdom. Language: English.

AB **Parathyroid hormone-related peptide** (PTHrP) is a regulatory protein associated with cell growth in non-osseous tissues and with osteoclast stimulation in bone. It has been implicated in the pathogenesis of bone metastases, particularly in breast carcinoma. PTHrP is widely expressed in primary prostate cancers, but there are few reports of its expression in prostatic metastases. The aim of this study was to examine the expression of PTHrP in bone metastases from patients with untreated adenocarcinoma of the prostate. Ten bone biopsies containing metastatic deposits of untreated prostatic cancer were identified. These were immunohistochemically stained for PTHrP using a murine **monoclonal antibody** (PTHLP[Ab1]) and the streptavidin-biotin complex technique. Intensity of staining for PTHrP was graded by two observers. In total, PTHrP expression was positive in 5/10 specimens. This was graded as moderate in four and weak in one. In those specimens with positive staining, the expression varied between cells. There was no obvious association between expression of PTHrP and tumour differentiation. PTHrP is expressed in prostatic bone metastases and may have a role in their pathogenesis and pathophysiology. However, expression is not universal.

L16 ANSWER 14 OF 41 CAPLUS COPYRIGHT 2005 ACS on STN

2001:661283 Document No. 135:240920 Tissue decomposition inhibitor. Saito, Hidemi; Tsunenari, Toshiaki; Onuma, Etsuro; Sato, Koh (Chugai Seiyaku K. K., Japan). PCT Int. Appl. WO 2001064249 A1 20010907, 131 pp. DESIGNATED STATES: W: CA, JP, US. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP5886 20000830. PRIORITY: JP 2000-52414 20000228.

AB A tissue decomposition inhibitor which contains a substance inhibiting the binding of a parathyroid hormone-associated peptide to its receptor. The

tissue decomposition inhibitor is a PTHrP receptor antagonist such as **antibody**, chimeric **antibody**, **monoclonal antibody**, or **antibody** fragment specifically binds to PTHrP receptor. The PTHrP receptor antagonist is useful for inhibiting decomposition muscle or adipose tissue and elevation of inflammatory cytokine. The PTHrP receptor antagonist is therefore useful for treating sepsis, trauma, muscle dystrophy, cancer-associated weight loss,.

L16 ANSWER 15 OF 41 CAPLUS COPYRIGHT 2005 ACS on STN

2001:64149 Document No. 134:126522 An osteoblast-derived inhibitor of osteoclast precursor formation for use in the treatment of bone diseases. Zhou, Hong; Kartsogiannis, Vassiliki; Hu, Yunshan; Gillespie, Matthew Todd; Ng, Kong Wah (St. Vincent's Institute of Medical Research, Australia). PCT Int. Appl. WO 2001005964 A1 20010125, 131 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-AU864 20000719. PRIORITY: AU 1999-1675 19990719.

AB This invention relates to a polypeptide factor which is able to inhibit the formation of osteoclasts. In particular, the invention relates to a factor which inhibits the differentiation of hematopoietic precursor cells into mononucleate osteoclast precursors. In a preferred form of the invention, the factor is a type (II) membrane polypeptide expressed on the osteoblast cell surface, which we have designated osteoclast inhibitory lectin (OCIL). Nucleic acids encoding the polypeptide factor, polypeptides, and **antibodies** to the polypeptide are disclosed and claimed. The factor is useful in the treatment of conditions associated with abnormalities of bone resorption.

L16 ANSWER 16 OF 41 CAPLUS COPYRIGHT 2005 ACS on STN

2001:31355 Document No. 134:99582 Remedies for drug-resistant hypercalcemia. Saito, Hidemi; Tsunenari, Toshiaki; Onuma, Etsuro (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2001002012 A1 20010111, 118 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP4523 20000706. PRIORITY: JP 1999-192270 19990706.

AB Remedies for drug-resistant hypercalcemia which contain as the active ingredient a substance inhibiting the binding of a **parathyroid hormone-related peptide** to its receptor. Therapeutics for drug-resistant hypercalcemia include bone resorption inhibitor (e.g. bisphosphates and/or calcitonin), calcium excretion promoter, intestinal calcium absorption inhibitor, or loop diuretic. The PTHrP and receptor-binding inhibitors are PTHrP receptor antagonist such as anti-PTHrP **antibodies** or fragments or chimeric **antibodies.**

L16 ANSWER 17 OF 41 CAPLUS COPYRIGHT 2005 ACS on STN

2001:105438 Document No. 134:278743 Human pancreatic adenocarcinomas express parathyroid hormone-related protein. Bouvet, Michael; Nardin, Stephanie R.; Burton, Douglas W.; Behling, Cynthia; Carethers, John M.; Moossa, A. R.; Deftos, Leonard J. (Department of Surgery, University of California, La Jolla, CA, 92161, USA). Journal of Clinical Endocrinology and Metabolism, 86(1), 310-316 (English) 2001. CODEN: JCEMAZ. ISSN: 0021-972X. Publisher: Endocrine Society.

AB PTH-related protein (PTHrP) is expressed in many common malignancies such as breast and prostate cancer and can regulate their growth. Little is known, however, about the role of PTHrP in pancreatic adenocarcinoma. To study PTHrP in pancreatic exocrine cancer, we studied its expression in pancreatic cancer cell lines and surgical specimens. Eight human pancreatic adenocarcinoma cell lines were evaluated: AsPC-1, BxPC-3, Capan-1, CFPAC-1, MIA PaCa-2, PANC-1, PANC-28, and PANC-48. Murine **monoclonal antibodies** to the amino-terminal (1-34), mid-region (38-64), and carboxyl-terminal peptides (109-141) of PTHrP were used to identify cellular PTHrP and secreted PTHrP, including Western blotting and immunocytochem. staining for PTHrP from each cell line. Cellular PTHrP was detected in all cell line exts. by both Western blotting and immunoassay. CFPAC-1, derived from a pancreatic liver metastasis, had the highest concentration of PTHrP, and MIA PaCa-2, derived from primary pancreatic adenocarcinoma, had the lowest. PTHrP was localized by immunocytochem. staining in the cytoplasm in all but one cell line, and both nuclear and cytoplasmic immunostaining were observed in the MIA PaCa-2 and PANC-1 cells. Secretion of PTHrP into cell medium was also observed for each cell line and paralleled intracellular PTHrP levels. Evidence for differential processing of PTHrP expression was provided by studies demonstrating different patterns of PTHrP among the cell lines when assessed by PTHrP immunoassays directed against different PTHrP peptides. In specific, PTHrP secretion measured by a PTHrP-(38-64) assay was highest for BxPC-3, whereas the highest levels of secreted PTHrP-(109-141) occurred in CFPAC-1 and PANC-1. Growth of AsPC-1 cells was stimulated in a dose-dependent manner by PTHrP-(1-34). Immunostaining from archival tissue of patients with pancreatic adenocarcinoma revealed strong PTHrP expression in all 14 specimens. All patients were eucalcemic preoperatively. These results demonstrate that PTHrP is commonly expressed in pancreatic cancer. Our data suggest that PTHrP may have growth-regulating properties in pancreatic adenocarcinoma cells, but further studies are required.

L16 ANSWER 18 OF 41 CAPLUS COPYRIGHT 2005 ACS on STN
2000:15036 Document No. 132:73627 Therapeutics containing inhibitors for **parathyroid hormone-related peptide** receptor for hypercalcemic crisis. Sato, Koh; Tsunenari, Toshiaki (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2000000219 A1 20000106, 120 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1999-JP3433 19990625. PRIORITY: JP 1998-180143 19980626.

AB Disclosed is a therapeutic composition containing an inhibitor for **parathyroid hormone-related peptide** receptor (PTHrP) for treating hypercalcemic crisis, that is frequently associated with malignant tumors, by using an antagonist such as an **antibody** to PTHrP. A nude mice or nude rat implanted with human pancreatic tumor-derived FA-6 cells or human lung cancer-derived LC-6-JCK cells was used as a disease model to evaluate the effects of the therapeutics to hypercalcemia of malignancy. Mouse **monoclonal antibody** number 23-57-137-1 and its humanized derivative hMBC(q) were used to demonstrate their rapid and long-lasting effects on reducing blood Ca level, which are more desirable as compared to calcitonin, in a rat model.

L16 ANSWER 19 OF 41 MEDLINE on STN
2000492584. PubMed ID: 10961900. Cell-cell contact between marrow stromal cells and myeloma cells via VCAM-1 and alpha(4)beta(1)-integrin enhances production of osteoclast-stimulating activity. Michigami T; Shimizu N;

Williams P J; Niewolna M; Dallas S L; Mundy G R; Yoneda T. (Division of Endocrinology and Metabolism, Department of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX 78284-7877, USA.) Blood, (2000 Sep 1) 96 (5) 1953-60. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Myeloma is a unique hematologic malignancy that exclusively homes in the bone marrow and induces massive osteoclastic bone destruction presumably by producing cytokines that promote the differentiation of the hematopoietic progenitors to osteoclasts (osteoclastogenesis). It is recognized that neighboring bone marrow stromal cells influence the expression of the malignant phenotype in myeloma cells. This study examined the role of the interactions between myeloma cells and neighboring stromal cells in the production of osteoclastogenic factors to elucidate the mechanism underlying extensive osteoclastic bone destruction. A murine myeloma cell line 5TGM1, which causes severe osteolysis, expresses alpha(4)beta(1)-integrin and tightly adheres to the mouse marrow stromal cell line ST2, which expresses the vascular cell adhesion molecule-1 (VCAM-1), a ligand for alpha(4)beta(1)-integrin. Co-cultures of 5TGM1 with primary bone marrow cells generated tartrate-resistant acid phosphatase-positive multinucleated bone-resorbing osteoclasts. Co-cultures of 5TGM1 with ST2 showed increased production of bone-resorbing activity and neutralizing **antibodies** against VCAM-1 or alpha(4)beta(1)-integrin inhibited this. The 5TGM1 cells contacting recombinant VCAM-1 produced increased osteoclastogenic and bone-resorbing activity. The activity was not blocked by the neutralizing **antibody** to known osteoclastogenic cytokines including interleukin (IL)-1, IL-6, tumor necrosis factor, or **parathyroid hormone-related peptide.** These data suggest that myeloma cells are responsible for producing osteoclastogenic activity and that establishment of direct contact with marrow stromal cells via alpha(4)beta(1)-integrin/VCAM-1 increases the production of this activity by myeloma cells. They also suggest that the presence of stromal cells may provide a microenvironment that allows exclusive colonization of myeloma cells in the bone marrow. (Blood. 2000;96:1953-1960)

L16 ANSWER 20 OF 41 MEDLINE on STN

2000260744. PubMed ID: 10803599. Enhanced growth of MCF-7 breast cancer cells overexpressing **parathyroid hormone-related peptide.** Falzon M; Du P. (Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston 77555, USA.. mfalzon@utmb.edu) . Endocrinology, (2000 May) 141 (5) 1882-92. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB PTH-related peptide (PTHrP) is a secreted protein produced by breast cancer cells both in vivo and in vitro. Because of its structural similarity to PTH at the amino terminus, the two proteins interact with a common cell surface receptor, the PTH/PTHrP receptor. When overproduced by tumor cells, PTHrP enters the circulation, giving rise to the common paraneoplastic syndrome of humoral hypercalcemia of malignancy. Although initially discovered in malignancies, PTHrP is now known to be produced by most cells and tissues in the body. It acts as an autocrine and paracrine mediator of cell proliferation and differentiation, effects which are mediated via the PTH/PTHrP receptor. Recent evidence also has shown that, directly after translation, PTHrP is able to enter the nucleus and/or nucleolus and influence cell cycle progression and apoptosis. In this study, we have either overproduced PTHrP or inhibited endogenous PTHrP production in the breast cancer cell line, MCF-7. Overexpression of PTHrP was associated with an increase in mitogenesis, whereas inhibiting endogenous PTHrP production resulted in decreased cell proliferation. The overexpressed peptide targeted to the perinuclear space. In contrast, PTHrP interaction with the cell surface PTH/PTHrP receptor resulted in decreased cell proliferation in the same cell line. This latter effect is dependent on interaction with the receptor, in that exogenously added PTHrP moieties known not to interact with the receptor had no effect on cell growth. Furthermore, neutralization of added peptide with an

anti-PTHrP antiserum completely abolished the growth inhibitory effects. In contrast, this **antibody** has no effect on the increased proliferation rate of the MCF-7 transfectants that overexpress PTHrP, compared with control cells. The net effect of autocrine/paracrine and intracrine effects of PTHrP in MCF-7 cells overproducing the peptide is accelerated cell growth. These findings have critical implications regarding the role of PTHrP in breast cancer, and they suggest that controlling PTHrP production in breast cancer may be useful therapeutically.

L16 ANSWER 21 OF 41 CAPLUS COPYRIGHT 2005 ACS on STN
1999:614132 Document No. 131:253353 Tumor-specific polypeptide-encoding nucleic acids and methods for therapy and diagnosis of lung cancer. Reed, Steven G.; Wang, Tongtong (Corixa Corporation, USA). PCT Int. Appl. WO 9947674 A2 19990923, 148 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US5798 19990317. PRIORITY: US 1998-40802 19980318; US 1998-40984 19980318; US 1998-123912 19980727; US 1998-123933 19980727.

AB Compds. and methods for the treatment and diagnosis of lung cancer are provided. The inventive compds. include polypeptides containing at least a portion of a lung tumor protein. Thus, 70 cDNA sequences were isolated from a human lung squamous cell carcinoma cDNA expression library and tumor-specific polypeptide-encoding cDNAs identified by subtraction with normal lung cDNA libraries and a cDNA library from normal liver and heart; an addnl. 16 cDNA clones were identified from a lung adenocarcinoma library. Vaccines and pharmaceutical compns. for immunotherapy of lung cancer comprising such polypeptides, or DNA mols. encoding such polypeptides, are also provided, together with DNA mols. for preparing the inventive polypeptides.

L16 ANSWER 22 OF 41 MEDLINE on STN
2000059573. PubMed ID: 10590360. Humoral hypercalcemia in patients with colorectal carcinoma: report of two cases and review of the literature. Lortholary A H; Cadeau S D; Bertrand G M; Guerin-Meyer V I; Gamelin E C; Audran M J. (Department of Medical Oncology, Centre Paul Papin, Angers, France.) Cancer, (1999 Dec 1) 86 (11) 2217-21. Ref: 17. Journal code: 0374236. ISSN: 0008-543X. Pub. country: United States. Language: English.

AB BACKGROUND: Humoral hypercalcemia rarely is associated with colorectal carcinoma; to the authors' knowledge only nine cases have been reported to date. METHODS: Two cases of advanced colorectal carcinoma with humoral hypercalcemia of malignancy (HHM) are presented. RESULTS: The two patients had severe hypercalcemia without bone metastases. The diagnosis of HHM was based on findings of hypercalcemia, hypophosphoremia, elevated serum **parathyroid hormone-related peptide** (PTHrP), and positive tumor immunoreactivity to **monoclonal** PTHrP antiserum. One patient had a colonic adenocarcinoma with a neuroendocrine component and the other patient had rectal adenocarcinoma. Immunoreactive PTHrP was found in both tumor components. Bisphosphonate treatment normalized the hypercalcemia within a few days but it recurred in the patients 2 weeks and 3 weeks later, respectively. The prognosis was extremely poor. CONCLUSIONS: To the authors' knowledge the two cases presented in the current study are the first to be reported with HHM-associated colorectal carcinoma with positive tumor immunoreactivity to PTHrP **monoclonal** antiserum. Copyright 1999 American Cancer Society.

L16 ANSWER 23 OF 41 MEDLINE on STN
2000056169. PubMed ID: 10588813. **Parathyroid hormone-related peptide** stimulates DNA synthesis and insulin

secretion in pancreatic islets. Villanueva-Penacarrillo M L; Cancelas J; de Miguel F; Redondo A; Valin A; Valverde I; Esbrit P. (Department of Metabolism, Fundacion Jimenez Diaz, Madrid, Spain.) Journal of endocrinology, (1999 Dec) 163 (3) 403-8. Journal code: 0375363. ISSN: 0022-0795. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Parathyroid hormone (PTH)-related protein (PTHrP) is present in the pancreatic islet. Recent data in transgenic mice suggest that PTHrP might modulate islet mass and insulin secretion. In the present study, we assessed the effect of the N-terminal PTH-like region of PTHrP on DNA synthesis in isolated rat islets. PTHrP (1-34), between 1 pM and 10 nM, for 48 h stimulated []thymidine incorporation into rat islets. This effect was maximally induced, about 2.5-fold over control, by 10 pM of this peptide, decreasing thereafter. In contrast, PTHrP (38-64) amide or PTHrP (107-139) were ineffective in increasing DNA synthesis in islets. Using reverse transcription followed by PCR, we confirmed that rat islets express PTHrP and the type I PTH/PTHrP receptor. Addition of a neutralizing anti-PTHrP **antibody** to the incubation medium of proliferating islets decreased islet DNA synthesis by 30%. The effect of a submaximal dose (30 pM) of PTHrP (1-34) on DNA synthesis in rat islets was abolished by 25 nM bisindolylmaleimide I, a protein kinase C (PKC) inhibitor, but not by 25 microM adenosine 3',5'-cyclic monophosphorothioate, Rp-isomer, a protein kinase A inhibitor. Moreover, 100 nM phorbol-12-myristate-13-acetate for 48 h also increased DNA synthesis 2-fold over controls in islets. PTHrP (1-34), at 100 nM, in contrast to 50 microM forskolin or 10 mM NaF, failed to affect adenylate cyclase activity in islet membranes. PTHrP, at 30 pM, was also found to increase 2-fold insulin released into the islet-conditioned medium within 24-48 h. Our results suggest that PTHrP is a modulator of pancreatic islet growth and/or function by a PKC-mediated mechanism.

L16 ANSWER 24 OF 41 MEDLINE on STN DUPLICATE 5

1999152338. PubMed ID: 10027900. Isolation and characterization of human clonogenic osteoblast progenitors immunoselected from fetal bone marrow stroma using STRO-1 **monoclonal antibody.** Oyajobi B O; Lomri A; Hott M; Marie P J. (INSERM Unite 349, Cell and Molecular Biology of Bone and Cartilage, Lariboisiere Hospital, Paris, France.) Journal of bone and mineral research : official journal of the American Society for Bone and Mineral Research, (1999 Mar) 14 (3) 351-61. Journal code: 8610640. ISSN: 0884-0431. Pub. country: United States. Language: English.

AB Osteoprogenitor cells present in human fetal bone marrow (BM) stroma have not been characterized. We used density gradient centrifugation, aggregation on binding lectin, and enrichment by magnetic activated cell sorting with STRO-1 **antibody** to isolate STRO-1+ cells from nonadherent human fetal BM stromal cells. Immunoselected STRO-1+ cells were immortalized using SV-40 large T antigen and a clone, F/STRO-1+ A, with weak alkaline phosphatase (ALP) activity was selected. The cloned cells proliferated rapidly but were not tumorigenic. Preconfluent F/STRO-1+ A cells showed immunoreactivity for osteopontin, alpha1(I) procollagen, and **parathyroid hormone-related peptide**, but not for the late osteoblast differentiation markers, osteocalcin (OC), or bone sialoprotein. However, differentiation of F/STRO-1+ A cells was induced by dexamethasone and 1,25-dihydroxyvitamin D3, as shown by increased ALP activity. In addition, osteogenesis occurred in F/STRO-1+ A cells cultured in three-dimentional aggregates, as assessed morphologically, histologically, and biochemically. Moreover, reverse transcription-polymerase chain reaction analysis showed that OC expression was silent in exponentially growing cells and occurred when cell-cell contacts were established in monolayer and in aggregates, showing induction of mature osteoblast phenotype by cell-cell contacts. Thus, clonal F/STRO-1+ A cells immunoselected from human fetal BM stroma display features of immature osteoprogenitor cells which can differentiate into mature osteogenic cells by cell-cell interactions or inducing agents. The generation by immunoselection of an immortalized clonogenic human fetal BM stroma-derived cell line which behaves like an osteoprogenitor cell provides a novel model system for identifying the signals required

for the commitment of osteoprogenitors in the human fetal BM stroma.

L16 ANSWER 25 OF 41 CAPLUS COPYRIGHT 2005 ACS on STN
1998:764302 Document No. 130:10622 **Antibody** to **parathyroid hormone-related peptide** (PTHrP) or the PTHrP receptor antagonist as a cancerous cachexia remedy. Sato, Koh; Tunenari, Toshiaki; Ishii, Kimie (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 9851329 A1 19981119, 125 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP2116 19980513. PRIORITY: JP 1997-125505 19970515; JP 1997-194445 19970718.
AB Disclosed is a cancerous cachexia remedy comprising a substance inhibiting the binding of a **parathyroid hormone-related peptide** (PTHrP) and its receptor, which inhibitor may consist of an antagonist against the receptor or an **antibody** to the PTHrP. Anti-cachexia effects of humanized mouse **monoclonal antibody** 23-57-137-1 were observed by using the nude mice transplanted with OCC-1 human buccal cancer cell, which effects were based on the blood level of Ca, body weight, and survival.

L16 ANSWER 26 OF 41 MEDLINE on STN DUPLICATE 6
1998225160. PubMed ID: 9556566. A negative vitamin D response DNA element in the human **parathyroid hormone-related peptide** gene binds to vitamin D receptor along with Ku antigen to mediate negative gene regulation by vitamin D. Nishishita T; Okazaki T; Ishikawa T; Igarashi T; Hata K; Ogata E; Fujita T. (Endocrine Genetics and Hypertension Unit, 4th Department of Internal Medicine, University of Tokyo School of Medicine, Bunkyo-ku, Tokyo 112, Japan.) Journal of biological chemistry, (1998 May 1) 273 (18) 10901-7. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB We found that the human **parathyroid hormone-related peptide** (hPTHrP) gene contained a DNA element (nVDREhPTHrP) homologous to a negative vitamin D response element in the human parathyroid hormone gene. It bound to vitamin D receptor (VDR) but not retinoic acid Xalpha receptor (RXRalpha) in the human T cell line MT2 cells. VDR binding to this element was confirmed by the Southwestern assay combined with immunodepletion using anti-VDR **monoclonal antibody**, and this binding activity was repressed by 1,25-dihydroxyvitamin D3. Such a repression was reversed by acid phosphatase treatment, suggesting that 1,25-dihydroxyvitamin D3 phosphorylates VDR to weaken its binding activity to nVDREhPTHrP. In electrophoretic mobility shift assay, we found anti-Ku antigen **antibody** specifically supershifted the MT2 nuclear proteinnVDREhPTHrP complex. The nVDREhPTHrP-bearing reporter plasmid produced vitamin D-dependent inhibition of the reporter activity in MT2 cells, which was markedly masked by the introduction of the Ku antigen expression vector in the antisense orientation. On the other hand, such a procedure did not perturb the vitamin D response element-mediated gene stimulation by vitamin D. These results indicate that nVDREhPTHrP interacts with Ku antigen in addition to VDR to mediate gene suppression by vitamin D.

L16 ANSWER 27 OF 41 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
1998:509009 Document No.: PREV199800509009. Epitope tag mapping of the extracellular and cytoplasmic domains of the rat parathyroid hormone (PTH)/PTH-related peptide receptor. Xie, Lin Y.; Abou-Samra, Abdul B. [Reprint author]. Endocrine Unit, Mass. Gen. Hosp., Harvard Med. Sch., Boston, MA 02114, USA. Endocrinology, (Nov., 1998) Vol. 139, No. 11, pp. 4563-4567. print.

CODEN: ENDOAO. ISSN: 0013-7227. Language: English.

AB The PTH-PTH-related peptide (PTHrP) receptor is predicted to span the plasma membrane seven times with an amino-terminal extracellular extension and a cytoplasmic carboxyl-terminal tail. To assess this prediction, we inserted 10- or 9-amino acid epitope tags from c-myc or hemophilus influenza hemaglutinin (HA), which are recognized by the **monoclonal antibodies** 9E10 and 12Ca5, respectively, in different extracellular and cytoplasmic regions of the receptor and examined the immunoreactivity of the epitopes in intact and permeabilized cells. The data show that the epitopes were well tolerated when introduced into the E2 region of the extracellular amino-terminus (E2-myc and E2-HA), in the first extracellular loop (EL1), in the second and third cytoplasmic loops (CL2c and CL3), or in the carboxyl-terminal tail (T-myc). Receptors tagged at these locations were well expressed, bound PTH with high affinity, and increased cAMP accumulation with a good efficiency. Receptors tagged in the second and third extracellular loops (EL2c and EL3c) or the fast cytoplasmic loop (CL1c) bound the PTH radioligand with a low affinity, stimulated cAMP accumulation with a low efficiency, and had low expression levels. The receptors tagged on presumed extracellular regions, E2-myc, E2-HA, EL1, EL2c, and EL3c, were readily detected on the surface of intact cells with the **monoclonal antibody** against the epitope tag. In contrast, receptors tagged with the c-myc epitope in the cytoplasmic loops (CL1c, CL2c, and CL3) or in the carboxyl-terminal tail (T-myc) did not show any 9E10 binding in intact cells. These receptors, however, were well expressed on the cell surface, as detected by the binding of the **monoclonal antibody**, 12Ca5, to the HA tag that was introduced into the E2 region of these constructs. The c-myc epitopes, however, became accessible after permeabilization of the cell membrane. In conclusion, these data provide experimental evidence for the sidedness of the extracellular and cytoplasmic domains of the PTH/ PTHrP receptor.

L16 ANSWER 28 OF 41 MEDLINE on STN DUPLICATE 7

1998215352. PubMed ID: 9556066. Role of interleukin-6 in uncoupling of bone in vivo in a human squamous carcinoma coproducing **parathyroid hormone-related peptide** and interleukin-6.

Nagai Y; Yamato H; Akaogi K; Hirose K; Ueyama Y; Ikeda K; Matsumoto T; Fujita T; Ogata E. (Biomedical Research Laboratories, Kureha Chemical Industry, Co., Ltd., Tokyo, Japan.) Journal of bone and mineral research : official journal of the American Society for Bone and Mineral Research, (1998 Apr) 13 (4) 664-72. Journal code: 8610640. ISSN: 0884-0431. Pub. country: United States. Language: English.

AB OCC tumor has been established from a human squamous carcinoma associated with humoral hypercalcemia of malignancy (HHM) and shown to overproduce **parathyroid hormone-related peptide** (PTHrP) and cause aggressive hypercalcemia when implanted into nude rats. In the present study, we have demonstrated by reverse transcription-polymerase chain reaction and Northern blot analysis that OCC tumor also overexpressed interleukin 6 (IL-6) mRNA and that tumor-bearing animals exhibited a marked increase in plasma IL-6 as well as PTHrP concentrations. When a **monoclonal antibody** against human IL-6 was injected to block the activities of tumor-derived IL-6, bone loss in tumor-bearing animals was significantly prevented. Quantitative bone histomorphometric analysis revealed that treatment with anti-IL-6 **antibody** caused a substantial decrease in both osteoclast number and eroded surface (as parameters of bone resorption) and also a significant increase in the mineral apposition rate, but little effect on the osteoblastic surface. These results provide in vivo evidence suggesting that in tumors coproducing IL-6 and PTHrP, IL-6 is involved not only in the acceleration of osteoclastic bone resorption but also, at least in part, in the suppression of osteoblastic functions in HHM syndrome.

L16 ANSWER 29 OF 41 MEDLINE on STN DUPLICATE 8

1998311968. PubMed ID: 9648162. Multiple organ failure associated with

extensive metastatic calcification in a patient with an intermediate state of human T lymphotropic virus type I (HTLV-I) infection: report of an autopsy case. Kumamoto H; Ichinohasama R; Sawai T; Naganuma H; Furukawa Y; Akiu N; Kano M; Ooya K. (Department of Oral Pathology, Tohoku University School of Dentistry, Sendai, Japan.. kumamoto@mail.cc.tohoku.ac.jp) . Pathology international, (1998 Apr) 48 (4) 313-8. Journal code: 9431380. ISSN: 1320-5463. Pub. country: Australia. Language: English.

AB A patient with an intermediate state of human T lymphotropic virus type I (HTLV-I) infection and in whom autopsy showed multiple organ failure (MOF) associated with extensive metastatic calcification in systemic organs is described. A 56-year-old man presented with signs and symptoms of advanced cardiac insufficiency, respiratory disturbance and renal failure. Serologically, the anti-human T lymphotropic virus type I (HTLV-I) **antibody** titer and the levels of both calcium and **parathyroid hormone-related peptide** (PTHrP) were distinctly elevated. These data suggested a diagnosis of adult T cell lymphoma/leukemia (ATLL). However, examination of a peripheral blood sample revealed only a few atypical lymphoid cells (3%) associated with mild leukocytosis (white blood cell count, 13.7 x 10(3)/mm3). Lymph node swelling was systemic but mild, with some nodes up to 10 mm in diameter. The patient died of MOF. Adult T cell leukemia/lymphoma was unable to be diagnosed definitively because of the short duration of laboratory abnormalities and because of the discrepancy between the laboratory data and the magnitude of lymphoproliferation in both the lymph nodes and peripheral blood. At autopsy, the most conspicuous finding was extensive metastatic calcification in the multiple organs, including the heart, lungs, kidneys, tongue, liver, pancreas, spleen and systemic arterial walls. Very small numbers of medium-sized atypical lymphoid cells admixed with small reactive lymphocytes were identified in multiple organs, with no evidence of massive infiltration. Molecular analyses could not detect **monoclonal** integration of HTLV-I provirus DNA or monoclonality of T cell lineage cells. **Parathyroid hormone-related peptide** was demonstrated in the cytoplasm of the atypical lymphoid cells on immunohistochemical examination. The bone trabeculae generally showed distinct evidence of resorption associated with marked proliferation of osteoclasts. These findings suggested that the hypercalcemia in the present case was categorized as humoral hypercalcemia of malignancy rather than local osteolytic hypercalcemia.

L16 ANSWER 30 OF 41 MEDLINE on STN DUPLICATE 9

97289447. PubMed ID: 9144352. Synovial fluids from patients with osteoarthritis and rheumatoid arthritis contain high levels of **parathyroid hormone-related peptide.**
Kohno H; Shigeno C; Kasai R; Akiyama H; Iida H; Tsuboyama T; Sato K; Konishi J; Nakamura T. (Department of Orthopaedic Surgery, Graduate School of Medicine, Kyoto University, Sakyo, Japan.) Journal of bone and mineral research : official journal of the American Society for Bone and Mineral Research, (1997 May) 12 (5) 847-54. Journal code: 8610640. ISSN: 0884-0431. Pub. country: United States. Language: English.

AB High levels of immunoreactive and biologically active **parathyroid hormone-related peptide** (PTHrP) were detected in synovial fluids from patients with osteoarthritis (OA) and rheumatoid arthritis (RA). The levels of PTHrP immunoreactivity in synovial fluids, measured by a two-site immunoradiometric assay (IRMA) which detects hPTHrP(1-72) or longer peptides and a radioimmunoassay (RIA) specific to the carboxy-terminal portion of hPTHrP, were 3.2 +/- 0.3 pmol of hPTHrP(1-86)/l and 61 +/- 7.0 pmol of hPTHrP(109-141)/l in OA patients (mean +/- SE, n = 23), and 4.8 +/- 0.8 pmol of hPTHrP(1-86)/l and 164 +/- 30 pmol of hPTHrP(109-141)/l in RA patients (n = 26). Synovial fluid PTHrP levels distributed above the normal plasma reference ranges in each assay (0.7-2.6 pmol of hPTHrP(1-86)/l; 16-60.6 pmol of hPTHrP(109-141)/l). After concentration using sequential cation-exchange and reverse-phase chromatography, synovial fluid exhibited the activity that stimulated cyclic adenosine monophosphate (cAMP) accumulation in osteoblastic ROS

17/2.8 cells expressing PTH/PTHrP receptors. The cAMP accumulation activity in synovial fluid was sensitive to coincubation with excess hPTHrP(3-40), a PTH/PTHrP receptor antagonist, and was completely neutralized by preincubation with a **monoclonal antibody** specific to hPTHrP but not PTH. Immunohistochemical analysis of RA synovium revealed that PTHrP was localized in fibroblast-like cells in the synovial pannus invading articular cartilage. Our data show that PTHrP is produced locally by the diseased synovial tissue and released into synovial fluid at high concentrations, allowing us to hypothesize that PTHrP plays a novel role as a paracrine/autocrine factor in the pathology of OA and RA.

L16 ANSWER 31 OF 41 MEDLINE on STN DUPLICATE 10

96279181. PubMed ID: 8663213. Identification and characterization of 1,25-dihydroxyvitamin D3-responsive repressor sequences in the rat **parathyroid hormone-related peptide** gene. Kremer R; Sebag M; Champigny C; Meerovitch K; Hendy G N; White J; Goltzman D. (Department of Medicine, McGill University, Montreal, Quebec H3A 1A1, Canada.) Journal of biological chemistry, (1996 Jul 5) 271 (27) 16310-6. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB **Parathyroid hormone-related peptide** (PTHRP) gene transcription is suppressed by 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), the active metabolite of vitamin D3. In the present report, we examined 1, 25(OH)2D3-mediated repression of PTHRP expression by transfection of PTHRP promoter/reporter constructs in normal human keratinocytes and by DNA binding. We localized an element conferring 1, 25(OH)2D3-mediated repression in vivo to a 47-base pair (bp) region located -1121 to -1075 from the transcriptional start site. Mobility shift analysis revealed that this vitamin D response element (VDRE) forms DNA-protein complexes. The addition of a **monoclonal antibody** that recognizes the DNA binding region of the vitamin D receptor (VDR) attenuated binding of the receptor to the 47-bp sequence, whereas the addition of **monoclonal antibody** raised against the retinoid X receptor (RXR) further retarded the mobility of the protein-DNA complex. Consequently, the PTHRP promoter element binds a VDR.RXR heterodimer. Examination of this VDRE revealed complete sequence homology with a half-site of the human and rat osteocalcin VDRE (GGGTGA). Furthermore, mutation analysis suggests that a 16-bp domain consisting of an almost perfect repeat separated by a 3-base pair "spacer" GGGTGGAGAGGGGTGA is responsible for the DNA-protein interaction within this 47-bp sequence. Our results therefore indicate the existence of an inhibitory VDRE within the PTHRP promoter that is similar in sequence composition and cellular factor requirement to classical up-regulatory VDREs.

L16 ANSWER 32 OF 41 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 11

95055300 EMBASE Document No.: 1995055300. Hypercalcemia and cosecretion of interleukin-6 and **parathyroid hormone related peptide** by a human renal cell carcinoma implanted into nude mice. Weissglas M.; Schamhart D.; Lowik C.; Papapoulos S.; Vos P.; Kurth K.-H.. Department of Urology, University Hospital Leiden, P.O. Box 9600,2300 RC Leiden, Netherlands. Journal of Urology Vol. 153, No. 3 I, pp. 854-857 1995.
ISSN: 0022-5347. CODEN: JOURAA
Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 950308

AB Humoral hypercalcemia of malignancy is a paraneoplastic syndrome believed to be due to production by the tumor of substances that stimulate osteoclastic bone resorption primarily. The human renal cell carcinoma cell line RC-8, grown in nude mice, was investigated for factors involved in renal cancer-induced hypercalcemia. At a tumor load of 200 to 400 mm3 the mice developed hypercalcemia and hypophosphatemia associated with a rise in serum 1,25-dihydroxyvitamin D concentration and cachexia. The

tumor released 1) significant amounts of human interleukin-6 (IL-6) and 2) **parathyroid hormone- related peptide** (PTHrP) into the circulation. Cancer cells further expressed mRNA for both human IL-6 and PTHrP. No secretion of human tumor necrosis factor-α or interleukin-1β could be demonstrated in the circulation of the host. **Antibodies** to IL-6 caused a significant ($p = 0.043$) inhibition of tumor growth and decreased serum calcium concentrations compared with control animals. Our data suggest that IL-6 is involved, either directly or indirectly, in the development of hypercalcemia in renal cell carcinoma.

L16 ANSWER 33 OF 41 MEDLINE on STN DUPLICATE 12
96013383. PubMed ID: 7573236. Expression of **parathyroid hormone-related peptide** and its receptor messenger ribonucleic acid in human amnion and chorion-decidua: implications for secretion and function. Bruns M E; Ferguson J E 2nd; Bruns D E; Burton D W; Brandt D W; Juppner H; Segre G V; Deftos L J. (Department of Pathology, University of Virginia, Charlottesville, USA.) American journal of obstetrics and gynecology, (1995 Sep) 173 (3 Pt 1) 739-46. Journal code: 0370476. ISSN: 0002-9378. Pub. country: United States. Language: English.

AB OBJECTIVE: Our purpose was to define the location and packaging of **parathyroid hormone-related peptide** in amnion-chorion and the potential target tissues for its action in fetal membranes. STUDY DESIGN: We studied fetal membranes by use of light microscopic immunocytochemistry with three **monoclonal antibodies** against distinct regions of the **parathyroid hormone-related peptide** molecule. For electron microscopy immunogold analysis with a **monoclonal antibody** specific to the 109-141 fragment was used to observe **parathyroid hormone-related peptide** intracellularly in amnion membrane and in the chorion layers. Multiplex reverse transcriptase-polymerase chain reaction with Southern blotting was used to identify parathyroid hormone/**parathyroid hormone -related peptide** receptor and control messenger ribonucleic acids in amnion and chorion-decidua. RESULTS: All **monoclonal antibodies** revealed immunoreactive **parathyroid hormone-related peptide** in the amniotic epithelial cells and in some fibroblast-like cells embedded in the extracellular matrix of the amnion. **Parathyroid hormone-related peptide** was also found in the chorion in fibroblast and trophoblast layers and in decidua. Ultrastructurally immunogold particles were evenly distributed throughout the amniotic epithelial cells and were present in apical microvilli and near the basal membranes. Electron microscopy studies of the chorion cytotrophoblast also showed freely dispersed immunogold particles of **parathyroid hormone-related peptide** with no packaging in secretory granules. Low to undetectable levels of parathyroid hormone/**parathyroid hormone-related peptide** receptor messenger ribonucleic acid were found in amnion tissue, whereas abundant receptor messenger ribonucleic acid was found in chorion-decidua. CONCLUSIONS: These results suggest the presence of a **parathyroid hormone-related peptide** paracrine system within the human fetal membranes.

L16 ANSWER 34 OF 41 MEDLINE on STN DUPLICATE 13
95051297. PubMed ID: 7962324. Development of a sensitive two-site immunoradiometric assay for **parathyroid hormone-related peptide**: evidence for elevated levels in plasma from patients with adult T-cell leukemia/lymphoma and B-cell lymphoma. Ikeda K; Ohno H; Hane M; Yokoi H; Okada M; Honma T; Yamada A; Tatsumi Y; Tanaka T; Saitoh T; +. (Fourth Department of Internal Medicine, University of Tokyo School of Medicine, Japan.) Journal of clinical endocrinology and metabolism, (1994 Nov) 79 (5) 1322-7. Journal code: 0375362. ISSN: 0021-972X. Pub. country: United States. Language: English.

AB We have developed a sensitive immunoradiometric assay for PTH-related peptide (PTHrP) using a **monoclonal antibody** against PTHrP(1-34) and a polyclonal **antibody** against PTHrP(50-83), with recombinant human PTHrP(1-87) as the standard. The detection limit of the immunoradiometric assay was 0.5 pmol/L, and plasma PTHrP(1-87) concentrations in 110 healthy subjects were 0.8 +/- 0.01 pmol/L, with the upper limit of the normal range being 1.1 pmol/L. Increased circulating PTHrP(1-87) concentrations were demonstrated in all 46 cancer patients with hypercalcemia, but not in patients with primary hyperparathyroidism, chronic renal failure, or hypoparathyroidism. Normalization of serum calcium levels after resection of tumors was shown to correlate well with that of plasma PTHrP(1-87) concentrations in 2 cancer patients. High circulating PTHrP(1-87) levels were also demonstrated in 12 out of 13 hypercalcemic patients with adult T-cell leukemia/lymphoma and in 7 out of 8 hypercalcemic patients with non-Hodgkin's lymphoma especially of B-cell type. These results suggest that PTHrP is a major humoral factor responsible for the hypercalcemia frequently associated with adult T-cell leukemia/lymphoma and also with B-cell lymphoma.

L16 ANSWER 35 OF 41 MEDLINE on STN DUPLICATE 14
93279241. PubMed ID: 8099324. Interleukin-2 increases production and secretion of **parathyroid hormone-related peptide** by human T cell leukemia virus type I-infected T cells: possible role in hypercalcemia associated with adult T cell leukemia. Ikeda K; Okazaki R; Inoue D; Ohno H; Ogata E; Matsumoto T. (Fourth Department of Internal Medicine, University of Tokyo School of Medicine, Japan.) Endocrinology, (1993 Jun) 132 (6) 2551-6. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB Although **parathyroid hormone-related peptide** (PTHRP) is produced by adult T cell leukemia (ATL) cells and causes hypercalcemia in ATL patients, very little is known about the regulation of PTHRP gene expression in the leukemic cells. The present study was undertaken to clarify the role of T cell growth factor, interleukin-2 (IL-2), in the expression of PTHRP gene, using a human T cell leukemia virus type I (HTLV-I)-infected T cell line, MT-2. Recombinant human IL-2 caused a transient increase in the steady state level of PTHRP messenger RNA (mRNA) in MT-2 cells, and a maximal effect was observed at 3-6 h. The effect of IL-2 was dose dependent, with a maximal response being observed at 10(-10) M. A **monoclonal antibody** against IL-2 receptor (anti-Tac **antibody**) inhibited the IL-2-induced increase in PTHRP mRNA level. Recombinant human IL-1, IL-3, IL-4, and IL-6 failed to increase PTHRP mRNA level. Nuclear run-off transcription assay showed that the transcription rate of the PTHRP gene was modestly increased by IL-2. In addition, IL-2 caused a substantial increase in the stability of PTHRP mRNA, compared with control cells in which the apparent half-life of PTHRP mRNA was less than 30 min after RNA synthesis was inhibited by the RNA polymerase II inhibitor, dichlorobenzimidazole riboside. The secretion of PTHRP, as determined by both a newly established immunoradiometric assay using recombinant human PTHRP(1-87) as the standard and an RIA using an **antibody** against PTHRP(109-141), was increased by IL-2 but not by IL-1, IL-3, IL-4, or IL-6. The IL-2-induced increase in PTHRP secretion was completely inhibited by the addition of anti-Tac **antibody.** These results demonstrate that IL-2 stimulates the production and secretion of PTHRP by HTLV-I-infected T cells through specific binding to IL-2 receptor and that the effect of IL-2 is mediated by a posttranscriptional as well as a transcriptional mechanism. It is suggested that IL-2 may be involved in an auctocrine/paracrine fashion not only in the proliferation of HTLV-I-infected T cells but also in the enhanced production and secretion of PTHRP and thus the development of hypercalcemia in ATL patients.

L16 ANSWER 36 OF 41 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
93233261 EMBASE Document No.: 1993233261. Reactive human bile ductules express **parathyroid hormone-related**

peptide. Roskams T.; Campos R.V.; Drucker D.J.; Desmet V.J.. Laboratory of Histo-/Cytochemistry, University of Leuven, Minderbroedersstraat 12,3000 Leuven, Belgium. Histopathology Vol. 23, No. 1, pp. 11-19 1993.
ISSN: 0309-0167. CODEN: HISTDD
Pub. Country: United Kingdom. Language: English. Summary Language: English.
ED Entered STN: 930912
AB Various cholestatic liver diseases as well as regeneration after submassive necrosis are accompanied by a striking increase in the number of bile ductules. These reactive bile ductules are thought to arise either from proliferation of pre-existing bile ductules or bile ductule-related facultative stem cells, or from ductular metaplasia of hepatocytes. Recently, we found that reactive bile ductules display neuro-endocrine features, and speculated that the substance(s), produced in the neuro-endocrine granules, might play a role in their growth and/or differentiation through an autocrine or paracrine pathway.
Parathyroid hormone-related peptide
has been shown to be encoded by a growth factor-regulated gene that may play a role in cell growth and differentiation. We studied the immunohistochemical expression of this peptide in human liver, including three normal biopsies, 11 cases of cholestatic liver disease, six cases of focal nodular hyperplasia and three cases of regenerating liver. In regenerating liver, primary biliary cirrhosis, primary sclerosing cholangitis and partial or intermittent obstruction, the majority of reactive ductular cells expressing neuro-endocrine markers also expressed **parathyroid hormone-related peptide.**
In focal nodular hyperplasia, a smaller number of bile ductular cells expressed the peptide. These findings suggest that **parathyroid hormone-related peptide** is localized in bile
ductular cells and may indicate a role for this hormone in the growth and/or differentiation of human reactive bile ductules.

L16 ANSWER 37 OF 41 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
1992:451455 The Genuine Article (R) Number: JF001. **PARATHYROID HORMONE-RELATED PEPTIDE** CAN REGULATE THE GROWTH OF HUMAN LUNG-CANCER CELLS, AND MAY FORM PART OF AN AUTOCRINE TGF-ALPHA LOOP. BURTON P B J (Reprint); KNIGHT D E. KINGS COLL, DIV BIOCHEM SCI, LONDON W8 7AH, ENGLAND (Reprint). FEBS LETTERS (6 JUL 1992) Vol. 305, No. 3, pp. 228-232. ISSN: 0014-5793. Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB **Parathyroid hormone-related peptide** (PTHrP) and transforming growth factor-alpha (TGF-alpha) were found to stimulate proliferation of human lung cancer cells (BEN-57). TGF-alpha stimulated PTHrP secretion from these cells. The polyclonal antisera raised against PTHrP significantly inhibited the growth of BEN-57 cells, and also the proliferation induced by TGF-alpha. Treatment of cells for up to 10 days with either a PTHrP receptor antagonist (PTHrP(7-34)) or PTHrP antiserum significantly inhibited the subsequent growth of these cells. We suggest that PTHrP may be a component of a complex autocrine loop involving TGF-alpha.

L16 ANSWER 38 OF 41 CAPLUS COPYRIGHT 2005 ACS on STN
1993:578924 Document No. 119:178924 Variable region sequence analysis of **monoclonal antibodies** raised to parathyroid hormone related protein (PTHrP). Rapley, Ralph; Walsh, David J.; Walker, Matthew R. (Dep. Clin. Biochem., Birmingham Univ., Birmingham, B15 2TH, UK). Eur. Biotechnol. Today, 223-8. Editor(s): Malvasi, Fabio; Cortese, Riccardo; Albertini, Alberto. Intercept: Andover, UK. (English) 1992. CODEN: 59HHAE.
AB Igs are synthesized from rearranged germline sequences encoding discrete structural and functional domains. It is essential to be able to rapidly accumulate nucleotide sequence data which may be used in the increasingly

reliable computer modeling based upon three-dimensional structural data. As a model system to investigate **monoclonal antibody** affinity at the nucleotide sequence level, the authors investigated a panel of murine MAbs raised to the 1-34 synthetic peptide of human **parathyroid hormone related peptide** (PTHrP). Based on peptide inhibition studies, these MAbs recognize identical epitopes with differing affinity, and have been used to quantitate PTHrP in attempts to establish its role as a mediator of humoral hypercalcemia of malignancy.

L16 ANSWER 39 OF 41 MEDLINE on STN DUPLICATE 15
92006179. PubMed ID: 1845254. Immunoreactivity of plasma parathyrin-related peptide: three region-specific radioimmunoassays and a two-site immunoradiometric assay compared. Ratcliffe W A; Norbury S; Stott R A; Heath D A; Ratcliffe J G. (Wolfson Research Laboratories, Department of Clinical Chemistry, Queen Elizabeth Medical Centre, Birmingham, U.K.) Clinical chemistry, (1991 Oct) 37 (10 Pt 1) 1781-7. Journal code: 9421549. ISSN: 0009-9147. Pub. country: United States. Language: English.
AB We measured parathyrin (**parathyroid hormone**)-**related peptide** (PTHRP) in plasma by three region-specific RIAs and compared them with an established two-site immunoradiometric assay (IRMA) of PTHRP1-86 in samples from control subjects and from patients with primary hyperparathyroidism (PH) and humoral hypercalcemia of malignancy (HHM). The two direct RIAs of PTHRP1-34 and PTHRP37-67 were specific for regions 9-18 and 52-61, respectively. In the extraction RIA of PTHRP1-34 we used an affinity gel containing a **monoclonal antibody** specific for the 17-27 sequence; cross-reacting PTHRP species eluted from the gel were assayed by the RIA of PTHRP1-34. PTHRP1-86 plasma concentrations by IRMA were less than 0.23 pmol/L in control subjects and patients with PH, and were significantly increased in patients with HHM (mean 6.1 pmol/L, P less than 0.001). In contrast, plasma PTHRP1-34 concentrations were not significantly different in the three groups; in HHM patients, the mean was 190 pmol/L. Plasma PTHRP37-67 concentrations were similar in control and PH groups and, although significantly increased in HHM patients (mean 440 pmol/L, P less than 0.002), showed poor diagnostic discrimination. PTHRP1-34 concentrations after affinity extraction of plasma were also significantly higher in HHM patients (mean 10.7 pmol/L, P less than 0.001), but showed incomplete diagnostic discrimination. We conclude that the diagnostic utility of the direct RIAs for quantifying PTHRP is markedly inferior to the IRMA of PTHRP1-86.

L16 ANSWER 40 OF 41 MEDLINE on STN DUPLICATE 16
91123763. PubMed ID: 1991989. Immunohistochemical localization of parathyroid hormone-related protein (PTHRP) in normal human skin. Atillasoy E J; Burtis W J; Milstone L M. (Department of Dermatology, Veterans Affairs Medical Center, West Haven, Connecticut 06516.) Journal of investigative dermatology, (1991 Feb) 96 (2) 277-80. Journal code: 0426720. ISSN: 0022-202X. Pub. country: United States. Language: English.
AB Human keratinocytes secrete large amounts of a **parathyroid hormone-related peptide** (PTHRP) in vitro. Because recent studies indicate that PTHRP could have a number of autocrine or paracrine functions in the skin, localization of this peptide in vivo is important. A **monoclonal** and two affinity-purified polyclonal **antibodies** were employed to locate PTHRP in normal human skin and cultivated human keratinocytes. PTHRP is present throughout the viable portion of the epidermis, in adnexal epithelial cells, and in all cultivated keratinocytes. These findings do not support the provocative suggestion that PTHRP is a marker for squamous differentiation.

L16 ANSWER 41 OF 41 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
1991:205774 Document No.: PREV199191108999; BA91:108999. A PATIENT OF CD4 NEGATIVE CD8 POSITIVE CHRONIC T-CELL LEUKEMIA ASSOCIATED WITH

HYPERCALCEMIA. TAMURA K [Reprint author]; SAGAWA K; KIMURA N; SATO H; KATAKAMI H; IMADA S; INOUE M. MIYAZAKI PREFECTURAL HOSP, 5-30 KITATAKAMATSU-CHO, MIYAZAKI 880, JPN. Leukemia Research, (1991) Vol. 15, No. 1, pp. 43-50.
CODEN: LEREDD. ISSN: 0145-2126. Language: ENGLISH.

AB A patient with chronic T-cell leukemia characterized by a suppressor phenotype is reported. A 71-year-old woman presented with symptoms and signs of hypercalcemia. Peripheral blood specimen showed abnormal lymphoid cells with an oval to cleaved nucleus, rather condensed chromatin, occasional prominent nucleolus, and basophilic cytoplasms with vacuoles which seems to be a T-cell counterpart of B-cell chronic lymphocytic leukemia with mixed cell types. The phenotype of these cells was CD4-, CD8+, CD5+, CD6+ with poor expression of CD3, CD7, and CD25. Southern blot analysis of T-cell receptor β-chain gene revealed one allele rearranged band. The serum **antibodies** were positive against human T-cell leukemia virus, type I-associated antigens, but **monoclonal** integration of proviral DNA was not detected in the leukemic cells suggesting that she was just a carrier of this virus. Interestingly, serum PTH-related peptide (PRP) was elevated. The combination therapy with vincristine and prednisolone for leukemia decreased not only the number of leukemic cells but also the serum PRP levels. The clinical course was aggressive. She only responded transiently to treatments, and died of renal failure due to uncontrollable hypercalcemia six weeks after admission.

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=> s l1 and PTHrP receptor
L18          0 L1 AND PTHRP RECEPTOR

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L19       5410 (OGATA E?/AU OR ONUMA E?/AU OR TSUNENARI T?/AU OR AZUMA Y?/AU)

=> s l19 and anti-PTHrP
L20         23 L19 AND ANTI-PTHRP

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L21          8 DUP REMOVE L20 (15 DUPLICATES REMOVED)

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L21 ANSWER 1 OF 8 MEDLINE on STN DUPLICATE 1

2005285209. PubMed ID: 15930357. Increased renal calcium reabsorption by parathyroid hormone-related protein is a causative factor in the development of humoral hypercalcemia of malignancy refractory to osteoclastic bone resorption inhibitors. **Onuma Etsuro**; **Azuma Yumiko**; Saito Hidemi; **Tsunenari Toshiaki**; Watanabe Toshihiko; Hirabayashi Manabu; Sato Koh; Yamada-Okabe Hisafumi; **Ogata Etsuro**. (Pharmaceutical Department IV, Chugai Research Laboratories, Chugai Pharmaceutical, Co., Ltd., Kanagawa, Japan.) Clinical cancer research : an official journal of the American Association for Cancer Research, (2005 Jun 1) 11 (11) 4198-203. Journal code: 9502500. ISSN: 1078-0432. Pub. country: United States. Language: English.

AB PURPOSE: Bisphosphonate and calcitonin lower blood calcium in humoral hypercalcemia of malignancy (HHM) by suppressing osteoclastic bone resorption, but repeated administration of these drugs often leads to relapse. In this study, we examined the roles of parathyroid hormone-related protein (PTHrP) in the development of bisphosphonate- and calcitonin-refractory HHM. EXPERIMENTAL DESIGN: Nude rats bearing the LC-6 JCK tumor xenograft (LC-6 rats) exhibited high bone turnover and HHM. Repeated administration of alendronate induced a sustained suppression of the bone resorption, but it caused only early and transient reduction of the blood calcium levels, leading to unresponsiveness to the drug. Because high blood levels of PTHrP were detected in the LC-6 rats, those that developed alendronate-refractory HHM were treated with an

anti-PTHrP antibody. RESULTS: Administration of **anti-PTHrP** antibody to animals that received repeated administration of alendronate, thereby developing alendronate-refractory HHM, resulted in an increase in fractional excretion of calcium and a marked decrease of blood calcium level. Drug-refractory HHM was also observed in animals that received another osteoclast inhibitor, an eel calcitonin analogue elcatonin. The blood calcium level decreased after the initial administration of elcatonin, but it eventually became elevated during repeated administration. Administration of the **anti-PTHrP** antibody, but not of alendronate, effectively reduced the blood calcium of the animals that developed elcatonin-refractory HHM. CONCLUSION: High levels of circulating PTHrP and the resulting augmentation of renal calcium reabsorption is one of the major causes of the emergence of osteoclast inhibitor-refractory HHM. Thus, blockage of PTHrP functions by a neutralizing antibody against PTHrP would benefit patients who develop bisphosphonate- or calcitonin-refractory HHM.

L21 ANSWER 2 OF 8 MEDLINE on STN DUPLICATE 2

2005311286. PubMed ID: 15800941. Parathyroid hormone-related protein (PTHrP) as a causative factor of cancer-associated wasting: possible involvement of PTHrP in the repression of locomotor activity in rats bearing human tumor xenografts. **Onuma Etsuro**; **Tsunenari Toshiaki**; Saito Hidemi; Sato Koh; Yamada-Okabe Hisafumi; **Ogata Etsuro.** (Pharmaceutical Research Department IV, Kamakura Research Laboratories, Chugai Pharmaceutical Co., Kanagawa, Japan.) International journal of cancer. Journal international du cancer, (2005 Sep 1) 116 (3) 471-8. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB Nude rats bearing the LC-6-JCK human lung cancer xenograft displayed cancer-associated wasting syndrome in addition to humoral hypercalcemia of malignancy. In these rats, not only PTHrP but also several other human proinflammatory cytokines, such as IL-6, leukemia-inducing factor, IL-8, IL-5 and IL-11, were secreted to the bloodstream. Proinflammatory cytokines induce acute-phase reactions, as evidenced by a decrease of serum albumin and an increase in alpha1-acid glycoprotein. Tumor resection abolished the production of proinflammatory cytokines and improved acute-phase reactions, whereas **anti-PTHrP** antibody affected neither proinflammatory cytokine production nor acute-phase reactions. Nevertheless, tumor resection and administration of **anti-PTHrP** antibody similarly and markedly attenuated not only hypercalcemia but also loss of fat, muscle and body weight. Body weight gain by **anti-PTHrP** antibody was associated with increased food consumption; increased body weight from **anti-PTHrP** antibody was observed when animals were freely fed but not when they were given the same feeding as those that received only vehicle. Furthermore, nude rats bearing LC-6-JCK showed reduced locomotor activity, less eating and drinking and low blood phosphorus; and **anti-PTHrP** antibody restored them. Although alendronate, a bisphosphonate drug, decreased blood calcium, it affected neither locomotor activity nor serum phosphorus level. These results indicate that PTHrP represses physical activity and energy metabolism independently of hypercalcemia and proinflammatory cytokine actions and that deregulation of such physiologic activities and functions by PTHrP is at least in part involved in PTHrP-induced wasting syndrome.

L21 ANSWER 3 OF 8 MEDLINE on STN DUPLICATE 3

2004546213. PubMed ID: 15517871. Generation of a humanized monoclonal antibody against human parathyroid hormone-related protein and its efficacy against humoral hypercalcemia of malignancy. **Onuma Etsuro**; Sato Koh; Saito Hidemi; **Tsunenari Toshiaki**; Ishii Kimie; Esaki Keiko; Yabuta Naohiro; Wakahara Yuji; Yamada-Okabe Hisafumi; **Ogata Etsuro.** (Chugai Research Laboratories, Chugai Pharmaceutical Co. Ltd., 200 Kajiwara, Kamakura, Kanagawa, Japan.) Anticancer research, (2004 Sep-Oct) 24 (5A) 2665-73. Journal code: 8102988. ISSN: 0250-7005. Pub. country: Greece. Language: English.

AB A humanized monoclonal antibody against parathyroid hormone-related protein (PTHrP) was generated from the mouse monoclonal antibody raised against the peptide corresponding to the N-terminal 34 amino acids of the human PTHrP [(PTHrP(1-34)]. The humanized antibody interacted with the PTHrP(1-34) with a kD value of 1.90 x 10(-10) M, and the epitope resides between the amino acids 20 and 30 of the PTHrP. PTHrP(1-34) significantly increased the intracellular cAMP levels in the rat osteosarcoma cells that expressed PTHR1, and the 5 microg/mL or higher concentrations of the humanized antibody almost completely blocked the PTHrP-induced cAMP production even in the presence of 2 microg/mL PTHrP(1-34), demonstrating its ability to fully neutralize PTHrP function. There was no significant difference in the potency of the mouse, chimera, or the humanized antibodies to suppress the PTHrP-induced increase in the intracellular cAMP in ROS cells. Furthermore, at the same doses, the administration of the chimera or the humanized antibody was equally effective in reducing the blood ionized calcium levels of hypercalcemic mice bearing the PAN-7-JCK human pancreatic cancer xenograft or the LC-6-JCK human lung cancer xenograft that secreted PTHrP. Thus, humanized **anti-PTHrP** may be useful for the treatment of the humoral hypercalcemia of malignancy in humans.

L21 ANSWER 4 OF 8 MEDLINE on STN DUPLICATE 4

2003534792. PubMed ID: 14613038. Treatment of malignancy-associated hypercalcemia and cachexia with humanized anti-parathyroid hormone-related protein antibody. Sato Koh; **Onuma Etsuro**; Yocum Richard C; **Ogata Etsuro.** (Department of International Coordination, Chugai Pharmaceutical Co, Ltd, Skizuuoka, Japan.) Seminars in oncology, (2003 Oct) 30 (5 Suppl 16) 167-73. Ref: 11. Journal code: 0420432. ISSN: 0093-7754. Pub. country: United States. Language: English.

AB Parathyroid hormone-related protein (PTHrP) plays a central role in humoral hypercalcemia of malignancy (HHM), which is one of the most frequent paraneoplastic syndromes. PTHrP produced by the tumor acts through a common PTH/PTHrP receptor to promote bone resorption, inhibit calcium excretion from the kidney, and induce hypercalcemia. Patients with HHM often develop cachexia associated with typical symptoms such as anorexia, malaise, nausea, constipation, polyuria, polydipsia, and confusion. The etiology of the cachexia is not fully understood but is thought to be caused by hypercalcemia and various cytokines such as interleukin-6, tumor necrosis factor-alpha, leukemia inhibitory factor, and others. In this study, we investigated the role of PTHrP in hypercalcemia and cachexia in HHM by using humanized **anti-PTHrP** antibody. A mouse monoclonal antibody that binds to PTHrP amino acid sequence 1-34 and inhibits PTHrP function has been humanized to create a specific and potent agent for the treatment of patients with HHM. The mouse monoclonal antibody has been shown to have antihypercalcemic activity against nude mice bearing human tumors. Because a mouse antibody is highly immunogenic in human patients, the complementarity-determining regions from the mouse antibody were grafted into a human antibody. The resulting humanized antibody specifically recognizes PTHrP(1-34) and neutralizes PTHrP functions in vitro and in vivo. The humanized **anti-PTHrP** antibody was administered intravenously to HHM model animals bearing tumors such as LC-6 human lung carcinoma. These animals showed symptoms similar to those of patients with HHM (eg, hypercalcemia and cachexia). The humanized **anti-PTHrP** antibody-treated animals responded with normalization of blood ionized calcium level through an improvement of bone metabolism and calcium excretion. Moreover, the treated animals also showed an improvement in body weight, ultromotivity, metabolic alkalosis, food consumption, water intake, serum phosphorus, and renal function. Consequently, the humanized antibody-treated animals experienced complete resolution of hypercalcemia and cachexia. These results suggest that the humanized antibody would be an effective and beneficial agent for patients with HHM, and that PTHrP is a major pathogenetic factor of hypercalcemia and cachexia in patients with HHM.

L21 ANSWER 5 OF 8 MEDLINE on STN DUPLICATE 5
2003428817. PubMed ID: 12969787. Monoclonal antibody to parathyroid hormone-related protein induces differentiation and apoptosis of chondrosarcoma cells. Miyaji Takahiro; Nakase Takanobu; **Onuma Eturo**; Sato Koh; Myoui Akira; Tomita Tetsuya; Joyama Susumu; Ariga Kenta; Hashimoto Jun; Ueda Takafumi; Yoshikawa Hideki. (Department of Orthopaedic Surgery, Osaka University Medical School, 2-2 Yamadaoka, Suita 565-0871, Japan.. miyaji@ort.med.osaka-u.ac.jp) . Cancer letters, (2003 Sep 25) 199 (2) 147-55. Journal code: 7600053. ISSN: 0304-3835. Pub. country: Ireland. Language: English.

AB We investigated the effects of treatment with anti-parathyroid hormone-related protein (1-34) monoclonal murine antibody (**anti-PTHrP** MoAb) on apoptosis and the differentiation of chondrosarcoma HTB-94 cells. Treatment with **anti-PTHrP** MoAb accelerated apoptosis of HTB-94 cells in a dose-dependent manner, and **anti-PTHrP** MoAb also promoted the chondrogenic differentiation of HTB-94 cells. The induction of apoptosis by **anti-PTHrP** MoAb via imbalance of Bcl-2/Bax ratio and activation of caspase-3 may provide a mechanistic explanation for its potential antitumor effects. Our results suggest the possibility that **anti-PTHrP** MoAb may be beneficial as a new treatment for chondrosarcoma.

L21 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
2002:888597 Document No. 138:3671 Angiogenesis inhibitors that block binding of PTH-related peptide to its receptor for use as antitumor agents. Saito, Hidemi; **Tsunenari, Toshiaki**; **Onuma, Etsuro**; Kato, Atsuhiko; Suzuki, Masami (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2002092133 A1 20021121, 110 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2002-JP4586 20020510. PRIORITY: JP 2001-140659 20010510.

AB It is found out that angiogenesis can be inhibited by a substance which inhibits the binding of a parathyroid hormone-associated peptide (e.g. PTHrP) to its receptor. The angiogenesis inhibitors can be **anti-PTHrP** antibodies, antibody fragments, humanized or chimeric antibodies, PTH receptor antagonists, or antisense oligonucleotides specific to PTHrP. These modified **anti-PTHrP** antibodies and PTH receptor antagonists are useful as antitumor agents and bone metastasis inhibitors.

L21 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
2001:31355 Document No. 134:99582 Remedies for drug-resistant hypercalcemia. Saito, Hidemi; **Tsunenari, Toshiaki**; **Onuma, Etsuro** (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2001002012 A1 20010111, 118 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP4523 20000706. PRIORITY: JP 1999-192270 19990706.

AB Remedies for drug-resistant hypercalcemia which contain as the active ingredient a substance inhibiting the binding of a parathyroid hormone-related peptide to its receptor. Therapeutics for drug-resistant hypercalcemia include bone resorption inhibitor (e.g. bisphosphates and/or calcitonin), calcium excretion promoter, intestinal calcium absorption

inhibitor, or loop diuretic. The PTHrP and receptor-binding inhibitors are PTHrP° receptor antagonist such as **anti-PTHrP** antibodies or fragments or chimeric antibodies.

L21 ANSWER 8 OF 8 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2000:244979 Document No.: PREV200000244979. The possibility of utilizing humanized **anti-PTHrP** antibody as an anti-HHM/cachexia agent. **Onuma, Etsuro** [Reprint author]; Saito, H.; **Azuma, Y.**; Shimizu, N.; **Tsunenari, T.**; Sato, K.; **Ogata, E.** . Chugai Pharmaceutical, Shizuoka, Japan. Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 287. print.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 01-05, 2000.
ISSN: 0197-016X. Language: English.

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L22 50 L19 AND VASOPRESSIN

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L23 ANSWER 1 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
2001:31354 Document No. 134:110951 Remedies for diseases caused by PTH or PTHrP. **Ogata, Etsuro**; Sato, Koh; **Onuma, Etsuro**; **Tsunenari, Toshiaki**; Saito, Hidemi; **Azuma, Yumiko** (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2001002011 A1 20010111, 130 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP4414 20000703. PRIORITY: JP 1999-189793 19990702.
AB Provided are remedies for diseases caused by PTH or PTHrP. These remedies contain, as the active ingredient, an agonist or an antagonist binding to PTH receptor or PTHrP receptor or a substance binding to a ligand of such a receptor to thereby promote or inhibit the binding of the ligand to the receptor.

L23 ANSWER 2 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN
2001:31353 Document No. 134:114837 Agents for ameliorating low **vasopressin** level. **Ogata, Etsuro**; **Onuma, Etsuro** ; **Tsunenari, Toshiaki**; Saito, Hidemi; **Azuma, Yumiko** (Chugai Seiyaku Kabushiki Kaisha, Japan). PCT Int. Appl. WO 2001002010 A1 20010111, 114 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP4413 20000703. PRIORITY: JP 1999-189322 19990702.
AB Agents for ameliorating low **vasopressin** level which contain as the active ingredient a substance capable of inhibiting the binding of a parathyroid hormone-associated peptide to its receptor; and agents for ameliorating symptoms caused by a decrease in **vasopressin** level which contain as the active ingredient a substance capable of inhibiting

the binding of a parathyroid hormone-associated peptide to its receptor.

L23 ANSWER 3 OF 23 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2000222942 EMBASE Parathyroid hormone-related protein as a potential target of therapy for cancer-associated morbidity. **Ogata E.**. Dr. E. Ogata, Cancer Institute Hospital, Japanese Found. for Cancer Research, 1-37 Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan. Cancer Vol. 88, No. 12 SUPPL., pp. 2909-2911 15 Jun 2000.
Refs: 4.
ISSN: 0008-543X. CODEN: CANCAR
Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20000713

AB BACKGROUND. Proinflammatory cytokines are involved in the genesis of cancer-associated cachexia. Parathyroid hormone-related protein (PTHrP) is the causative agent in humoral hypercalcemia of malignancy (HHM) and is frequently secreted from various kinds of solid tumors as well as from adult T-cell leukemia/lymphoma. PTHrP, like PTH, acts on PTH receptor type 1 (PTH1R). Activation of PTH1R may lead to stimulation of secretion of proinflammatory cytokines. It is expected, therefore, that PTHrP constitutes a key factor in the activation of the proinflammatory and cachectogenic cytokine network and consequently in the development of cachexia in patients with cancer. METHODS. Two groups of cancer-bearing patients of similar clinical backgrounds were enrolled. Plasma concentrations of PTHrP and cytokines were measured with immunoradiometric assay and radioimmunoassay, respectively. Cancer tissues from patients with HHM were transplanted into nude mice or nude rats. The effects of humanized antihuman PTHrP antibody were examined RESULTS. In clinical studies, Group B patients (with elevated plasma PTHrP), compared with Group A patients (with normal plasma PTHrP), tended to exhibit higher plasma levels of tumor necrosis factor (TNF)-α (P = 0.13), interleukin(IL)-5 (P = 0.08), and IL-8 (P = 0.08), and had significantly higher levels of IL-6 (P = ≤0.01). The levels of TNF-α and IL-6 correlated with those of PTHrP. In animal studies, the antibody caused a prompt and sustained decline in serum calcium. This response was accompanied by improvements in food intake, drinking, body weight gain, and general behavior. It also ameliorated the suppression of serum ADH. When those effects were compared with those induced either by bisphosphonate or calcitonin, it turned out that not all of the beneficial effects of the antibody were directly correlated with the depression of blood calcium. CONCLUSIONS. PTHrP is a promising molecular target for the development of a novel mode of treatment for patients with cancer-associated morbidity. (C) 2000 American Cancer Society.

L23 ANSWER 4 OF 23 MEDLINE on STN DUPLICATE 1

97331237. PubMed ID: 9187569. A candidate case for lymphocytic infundibulo-neurohypophysitis mimicking a neurohypophysial tumor. Tsujii S; Takeuchi J; Koh M; Mizuta M; **Azuma Y**; Oishi M; Akazawa Y; Kuzuya H. (Department of Clinical Research, Kyoto National Hospital.) Internal medicine (Tokyo, Japan), (1997 Apr) 36 (4) 293-7. Journal code: 9204241. ISSN: 0918-2918. Pub. country: Japan. Language: English.

AB A 56-year-old Japanese man presented with a 2-month duration of polyuria and polydipsia. The diagnosis of diabetes insipidus was confirmed by water deprivation and **vasopressin** injection. The secretory function of the adenohypophysis was estimated as normal by a variety of provocative tests. Magnetic resonance imaging (MRI) displayed the loss of the hyperintense signal of the neurohypophysis and a tumor-like lesion confined to the neurohypophysis. The tissue specimen resected at transsphenoidal surgery showed diffuse lymphocytic infiltration. These findings suggest that this is a candidate case for lymphocytic infundibuloneurohypophysitis (LIN) that is not identical to classical lymphocytic hypophysitis. This patient will be followed up to determine whether this case simply represents an early stage of classical hypophysitis or a different clinical entity.

L23 ANSWER 5 OF 23 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1993:474411 The Genuine Article (R) Number: LP431. ROLE OF CALCIUM FLUXES IN THE ACTION OF GLUCAGON ON GLUCOSE-METABOLISM IN RAT HEPATOCYTES. MINE T (Reprint); KOJIMA I; **OGATA E.** UNIV TOKYO, SCH MED, DEPT INTERNAL MED 4, DIV GASTROENTEROL, 3-28-6 MEJIRODAI, BUNKYO KU, TOKYO 112, JAPAN (Reprint); GUNMA UNIV, INST ENDOCRINOL, MAEBASHI, GUNMA 371, JAPAN. AMERICAN JOURNAL OF PHYSIOLOGY (JUL 1993) Vol. 265, No. 1, Part 1, pp. G35-G42. ISSN: 0002-9513. Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The aim of the present study was to assess the role of calcium fluxes in the action of glucagon on glycogenolysis and gluconeogenesis in isolated rat hepatocytes. Calcium influx was blocked by two ways: by use of the compound tetramethrin and by reduction of extracellular calcium to 1 muM. The minimal concentration of tetramethrin that inhibited glucagon-mediated calcium entry was 7.5 X 10(-7) M. In the presence of 7.5 x 10(-7) M tetramethrin, glucagon-induced glycogenolysis was markedly attenuated when glucagon concentration was 10(-9) M or higher. In contrast, tetramethrin had no effect on glycogenolysis evoked by lower concentrations of glucagon. Similarly, tetramethrin greatly-reduced gluconeogenesis induced by high concentrations of glucagon without affecting the effect of low concentrations of glucagon. The same results were obtained in the presence of 1 muM extracellular calcium. To abolish glucagon-induced elevation of cytoplasmic free calcium concentration, we heavily loaded quin2 into hepatocytes. In these cells, glycogenolysis evoked by low concentrations of glucagon was completely abolished. Glycogenolysis caused by high concentrations of glucagon was markedly inhibited. These results indicate that glucagon action on hepatic glucose metabolism is mediated by two different mechanisms, which depend on concentrations of glucagon.

L23 ANSWER 6 OF 23 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1992:33039 The Genuine Article (R) Number: GX685. MECHANISM OF GLYCOGENOLYTIC ACTION OF HISTAMINE IN RAT HEPATOCYTES. MINE T (Reprint); KOJIMA I; **OGATA E.** UNIV TOKYO, SCH MED, DEPT INTERNAL MED 4, DIV GASTROENTEROL & BIOL, 3-28-6 MEJIRODAI, BUNKYO KU, TOKYO 112, JAPAN (Reprint); GUNMA UNIV, INST ENDOCRINOL, MAEBASHI, GUNMA 371, JAPAN. AMERICAN JOURNAL OF PHYSIOLOGY (DEC 1991) Vol. 261, No. 6, Part 1, pp. G1000-G1004. ISSN: 0002-9513. Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The mechanism by which histamine induces glycogenolysis was investigated in rat hepatocytes. Histamine induced stimulation of glucose output in hepatocytes in a dose-dependent manner. The maximal effect of the glycogenolytic action of histamine, which was approximately 60% of the maximal glucagon action, was obtained at 10(-6) M. These effects were inhibited by H-1 receptor antagonists triprolidine hydrochloride and tripelennamine but not by a H-2 receptor antagonist cimetidine. Histamine also increased the activity of phosphorylase a. When 10(-6) M histamine and 5 x 10(-9) M glucagon were added simultaneously, the actions of these two agents were additive. In contrast, there was no additivity when 10(-6) M histamine and 10(-8) M angiotensin II were added. Histamine did not increase adenosine 3',5'-cyclic monophosphate at any doses tested but induced a rapid increase in the cytoplasmic free calcium concentration ([Ca2+]c). Histamine increased [Ca2+]c even in the presence of 1-mu-M extracellular calcium, an observation suggesting that histamine caused calcium release from an intracellular calcium pool(s). When [H-3]inositol-labeled hepatocytes were incubated with histamine, radioactivity in the D-myo-inositol trisphosphate fraction was rapidly increased. These results indicate that histamine acts on rat hepatocytes mainly via H-1 receptors and stimulates glycogenolysis by activating the calcium messenger system.

L23 ANSWER 7 OF 23 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1991:304801 The Genuine Article (R) Number: FM778. HIGH POTASSIUM INTAKE ATTENUATES ANTINATRIURETIC RESPONSE TO AIR STRESS IN DOCA-SALT RATS. SATO Y (Reprint); ANDO K; **OGATA E**; FUJITA T. UNIV TOKYO, SCH MED, DEPT INTERNAL MED 4, 3-28-6 MEJIRODAI, BUNKYO KU, TOKYO 112, JAPAN. AMERICAN JOURNAL OF PHYSIOLOGY (MAY 1991) Vol. 260, No. 5, Part 2, pp. R941-R945. ISSN: 0002-9513. Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We studied the effects of potassium supplementation (2 wk of 0.5% KCl to drink) on responses of renal function to a stressful environmental stimulus (air stress) in deoxycorticosterone acetate (DOCA)-salt rats. In conscious DOCA-salt rats, air stress decreased urine flow rate and urinary sodium excretion without changes in effective renal plasma flow and glomerular filtration rate, whereas in normotensive vehicle-treated rats air stress had no effect on these measures. Renal denervation abolished the antidiuretic and antinatriuretic responses to air stress in DOCA-salt rats. Correspondingly potassium supplementation in DOCA-salt rats could not only reduce basal blood pressure significantly but also attenuate the antidiuretic and antinatriuretic responses to air stress without renal denervation. Evidence suggests that the attenuation by potassium supplementation of air stress-induced decrease in urine flow and sodium excretion in DOCA-salt rats may be partly involved in the natriuretic and the resultant antihypertensive actions of potassium in DOCA-salt hypertensive rats, but the mechanisms could not be clarified by the present study.

L23 ANSWER 8 OF 23 MEDLINE on STN DUPLICATE 2

92059486. PubMed ID: 1719825. Ion channel activities of cultured rat mesangial cells. Matsunaga H; Yamashita N; Miyajima Y; Okuda T; Chang H; **Ogata E**; Kurokawa K. (Fourth Department of Internal Medicine, University of Tokyo School of Medicine, Japan.) American journal of physiology, (1991 Nov) 261 (5 Pt 2) F808-14. Journal code: 0370511. ISSN: 0002-9513. Pub. country: United States. Language: English.

AB We used the patch-clamp technique to clarify the nature of ion channels in renal mesangial cells in culture. In the cell-attached mode most patches were silent in the absence of agonists. In some patches a 25-pS nonselective channel was observed. This 25-pS cation channel was consistently observed in inside-out patches, and it was activated by intracellular Ca2+. Excised patch experiments also revealed the existence of a 40-pS K+ channel, which was activated by intracellular Ca2+. This 40-pS K+ channel was observed infrequently in the cell-attached mode. The activities of both channels were increased by arginine **vasopressin** or angiotensin II, resulting from an increase in intracellular Ca2+ concentration.

L23 ANSWER 9 OF 23 MEDLINE on STN DUPLICATE 3

92026457. PubMed ID: 1718168. Endothelin 1 increases cell calcium in mouse collecting tubule cells. Naruse M; Uchida S; **Ogata E**; Kurokawa K. (First Department of Internal Medicine, University of Tokyo Faculty of Medicine, Japan.) American journal of physiology, (1991 Oct) 261 (4 Pt 2) F720-5. Journal code: 0370511. ISSN: 0002-9513. Pub. country: United States. Language: English.

AB Effects of endothelin 1 (ET-1) on intracellular free calcium concentration ([Ca2+]i) were examined in superfused single-nephron segments dissected from mouse kidney. ET-1, 10(-9) to 10(-6) M, caused a biphasic increase in [Ca2+]i consisting of an initial rapid rise followed by a second more sustained elevation in [Ca2+]i in cortical collecting tubules (CCT), outer medullary CT (OMCT), and inner medullary CT (IMCT). The magnitude of the response was dose dependent and was greater in CCT than in OMCT or IMCT. Additional studies using CCT revealed that Ca2+ removal from the superfusate resulted in attenuation of the second phase of [Ca2+]i with approximately 50% reduction in the height of the initial [Ca2+]i peak in response to 10(-6) M ET-1. Ca2+ channel blocker nicardipine had little

effect on ET-1-evoked changes in [Ca2+]i. BAY K 8644 and high superfusate K+ also did not affect [Ca2+]i. Addition of ET-1 and arginine **vasopressin** (AVP), 10(-6) M each, showed the presence of homologous desensitization but the absence of heterologous desensitization in [Ca2+]i changes. There was no additive effect of ET-1 and AVP on [Ca2+]i when they were added together. These data show that ET-1 evokes a biphasic increase in [Ca2+]i of collecting tubules and suggest that the initial peak of the ET-1-evoked rise in [Ca2+]i is largely due to cell Ca2+ release and that the second sustained rise in [Ca2+]i is largely due to increased Ca2+ influx. Data also suggest that ET-1 and AVP may act in the collecting tubules through different receptors.

L23 ANSWER 10 OF 23 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

92047083 EMBASE Document No.: 1992047083. Ion channel activities of cultured rat mesangial cells. Matsunaga H.; Yamashita N.; Miyajima Y.; Okuda T.; Chang H.; **Ogata E.**; Kurokawa K.. 1st Dept. of Internal Medicine, Univ. of Tokyo, School of Medicine, 7-3-1 Hongo,Bunkyoku, Tokyo 113, Japan. American Journal of Physiology - Renal Fluid and Electrolyte Physiology Vol. 261, No. 5 30-5, pp. F808-F814 1991.
ISSN: 0002-9513. CODEN: AJPFDM
Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 920320

AB We used the patch-clamp technique to clarify the nature of ion channels in renal mesangial cells in culture. In the cell-attached mode most patches were silent in the absence of agonists. In some patches a 25-pS nonselective channel was observed. This 25-pS cation channel was consistently observed in inside-out patches, and it was activated by intracellular Ca2+. Excised patch experiments also revealed the existence of a 40-pS K+ channel, which was activated by intracellular Ca2+. This 40-pS K+ channel was observed infrequently in the cell-attached mode. The activities of both channels were increased by arginine **vasopressin** or angiotensin II, resulting from an increase in intracellular Ca2+ concentration.

L23 ANSWER 11 OF 23 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

91340345 EMBASE Document No.: 1991340345. Endothelin 1 increases cell calcium in mouse collecting tubule cells. Naruse M.; Uchida S.; **Ogata E.**; Kurokawa K.. First Dept. Internal Medicine, University of Tokyo, School of Medicine, 7-3-1 Hongo,Bunkyo-ku, Tokyo 113, Japan. American Journal of Physiology - Renal Fluid and Electrolyte Physiology Vol. 261, No. 4 30-4, pp. F720-F725 1991.
ISSN: 0002-9513. CODEN: AJPFDM
Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 920316

AB Effects of endothelin 1 (ET-1) on intracellular free calcium concentration ([Ca2+](i)) were examined in superfused single-nephron segments dissected from mouse kidney. ET-1, 10-9 to 10-6 M, caused a biphasic increase in [Ca2+](i) consisting of an initial rapid rise followed by a second more sustained elevation in [Ca2+](i) in cortical collecting tubules (CCT), outer medullary CT (OMCT), and inner medullary CT (IMCT). The magnitude of the response was dose dependent and was greater in CCT than in OMCT or IMCT. Additional studies using CCT revealed that Ca2+ removal from the superfusate resulted in attenuation of the second phase of [Ca2+](i) with .apprx.50% reduction in the height of the initial [Ca2+](i) peak in response to 10-6 M ET-1. Ca2+ channel blocker nicardipine had little effect on ET-1-evoked changes in [Ca2+](i). BAY K 8644 and high superfusate K+ also did not affect [Ca2+](i). Addition of ET-1 and arginine **vasopressin** (AVP), 10-6 M each, showed the presence of homologous desensitization but the absence of heterologous desensitization in [Ca2+](i) changes. There was no additive effect of ET-1 and AVP on [Ca2+](i) when they were added together. These data show that ET-1 evokes a biphasic increase in [Ca2+](i) of collecting tubules and suggest that the initial peak of the ET-1-evoked rise in [Ca2+](i) is largely due to

cell Ca2+ release and that the second sustained rise in [Ca2+](i) is largely due to increased Ca2+ influx. Data also suggest that ET-1 and AVP may act in the collecting tubules through different receptors.

L23 ANSWER 12 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

1990:146963 Document No.: PREV199038068413; BR38:68413. **VASOPRESSIN** INCREASES INTRACELLULAR FREE CALCIUM BY STIMULATING CALCIUM ENTRY VIA V2 RECEPTOR IN CYCLIC AMP INDEPENDENT MANNER IN MOUSE CORTICAL OUTER AND MEDULLARY COLLECTING TUBULE CELLS. NARUSE M [Reprint author]; UCHIDA S; **OGATA E**; KUROKAWA K. IST DEP INT MED, UNIV TOKYO SCH MED, TOKYO, JPN. Kidney International, (1990) Vol. 37, No. 1, pp. 362.
Meeting Info.: MEETING OF THE AMERICAN SOCIETY OF NEPHROLOGY, WASHINGTON, D.C., USA, DECEMBER 3-6, 1989. KIDNEY INT.
CODEN: KDYIA5. ISSN: 0085-2538. Language: ENGLISH.

L23 ANSWER 13 OF 23 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1990:28451 The Genuine Article (R) Number: CG537. **VASOPRESSIN** INCREASES INTRACELLULAR FREE CA BY STIMULATING CA ENTRY VIA V2 RECEPTOR IN CAMP INDEPENDENT MANNER IN MOUSE CORTICAL, OUTER AND INNER MEDULLARY COLLECTING TUBULE CELLS. NARUSE M (Reprint); UCHIDA S; **OGATA E**; KUROKAWA K. UNIV TOKYO, SCH MED, DEPT INTERNAL MED 1, TOKYO 113, JAPAN; UNIV TOKYO, SCH MED, DEPT INTERNAL MED 6, TOKYO 113, JAPAN. KIDNEY INTERNATIONAL (JAN 1990) Vol. 37, No. 1, pp. 362-362. ISSN: 0085-2538. Publisher: BLACKWELL SCIENCE INC, 238 MAIN ST, CAMBRIDGE, MA 02142. Language: English.

L23 ANSWER 14 OF 23 MEDLINE on STN DUPLICATE 4

90078645. PubMed ID: 2592564. Ambient Cl- ions modify rat mesangial cell contraction by modulating cell inositol trisphosphate and Ca2+ via enhanced prostaglandin E2. Okuda T; Kojima I; **Ogata E**; Kurokawa K. (Fourth Department of Internal Medicine, University of Tokyo School of Medicine, Japan.) Journal of clinical investigation, (1989 Dec) 84 (6) 1866-72. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB Our recent observation showed that angiotensin II (AII) and arginine **vasopressin** (AVP) stimulate Ca2+-activated Cl- conductance in mesangial cells. These data raise the possibility that mesangial cell function may be modulated by extracellular chloride concentration [(Cl-]o). The present study was undertaken to test this possibility using cultured rat mesangial cells. When the [Cl-]o was reduced to zero, the percentage of mesangial cells showing contraction responding to AII and AVP was decreased from 72 +/- 9 to 33 +/- 10% and from 60 +/- 4 to 24 +/- 11%, respectively. Ca2+ transients induced by AII and AVP, measured in mesangial cells loaded with Ca2+-sensitive photoprotein aequorin, were attenuated as [Cl-]o decreased. Also, when [Cl-]o decreased, inositol trisphosphate (IP3) levels of mesangial cells were suppressed, both in the presence and absence of AII or AVP. PGE2 production by mesangial cells increased when [Cl-]o decreased and the effects of ambient Cl- deprivation could be restored by addition of indomethacin to the Cl- -free medium. Moreover, PGE2 decreased mesangial cell contractility, Ca2+ transients, and IP3 production in response to AII and AVP. These data suggest that the decrease in [Cl-]o attenuates mesangial cell contraction by suppressing IP3 production and thus Ca2+ transients in response to AII and AVP through enhanced PGE2 production.

L23 ANSWER 15 OF 23 MEDLINE on STN DUPLICATE 5

89325143. PubMed ID: 2546739. Stimulation of glucose production by activin-A in isolated rat hepatocytes. Mine T; Kojima I; **Ogata E** . (Fourth Department of Internal Medicine, University of Tokyo School of Medicine, Japan.) Endocrinology, (1989 Aug) 125 (2) 586-91. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB The effect of activin-A on glycogenolysis was studied in isolated rat

hepatocytes. Activin-A stimulated glucose output in hepatocytes in a dose-dependent manner. The maximal effect of the glycogenolytic action of activin-A, which was about 50% of the glucagon action, was obtained at 10(-9) M. When 10(-9) M activin-A and 5 x 10(-9) M glucagon were added simultaneously, the actions of these two agents were additive. In contrast, there was no additivity when 10(-9) M activin-A and 10(-8) M angiotensin-II were added. Activin-A did not increase cAMP at any doses tested, but induced a rapid increase in cytoplasmic free calcium concentration. Activin-A increased the cytoplasmic free calcium concentration even in the presence of 1 microM extracellular calcium, suggesting that activin-A caused calcium release from an intracellular calcium pool(s). The internal calcium pool affected by activin-A appeared to be the same as that affected by either angiotensin-II or **vasopressin.** When [3H] inositol-labeled hepatocytes were incubated with activin-A, radioactivity in the inositol trisphosphate fraction was rapidly increased. These results indicate that activin-A acts on rat hepatocytes and stimulates glycogenolysis by activating the calcium messenger system.

L23 ANSWER 16 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

1989:87695 Document No.: PREV198936043786; BR36:43786. VASODILATORY ACTIONS OF CALCITONIN GENE-RELATED PEPTIDE AND CALCIUM EFFECTS IN FOREARM VASCULAR BEDS. FUJITA T [Reprint author]; ITO Y; ISAKA M; NODA H; SATO Y; **OGATA E.** 4TH DEP INT MED, FAC MED, UNIV TOKYO, TOKYO 112, JAPAN. Circulation, (1988) Vol. 78, No. 4 PART 2, pp. II403. Meeting Info.: 61ST SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION, WASHINGTON, D.C., USA, NOVEMBER 14-17, 1988. CIRCULATION. CODEN: CIRCAZ. ISSN: 0009-7322. Language: ENGLISH.

L23 ANSWER 17 OF 23 MEDLINE on STN DUPLICATE 6

88252215. PubMed ID: 2454673. Evidence of cyclic AMP-independent action of glucagon on calcium mobilization in rat hepatocytes. Mine T; Kojima I; **Ogata E.** (Fourth Department of Internal Medicine, University of Tokyo School of Medicine, Japan.) Biochimica et biophysica acta, (1988 Jun 30) 970 (2) 166-71. Journal code: 0217513. ISSN: 0006-3002. Pub. country: Netherlands. Language: English.

AB Glucagon increases the cytoplasmic free calcium concentration as measured by aequorin bioluminescence. It has been proposed by Wakelam et al. (Nature 323 (1986) 68-71) that low concentrations of glucagon mobilize calcium from an intracellular pool by causing polyphosphoinositide breakdown. To identify whether cyclic AMP mediates changes in the cytoplasmic free calcium concentration ([Ca2+]c) induced by glucagon, the effects of forskolin and exogenous cyclic AMP on [Ca2+]c were compared with that of glucagon in aequorin-loaded hepatocytes. Although the magnitudes of the [Ca2+]c responses to 250 microM forskolin and 1 mM 8-bromo cyclic AMP were identical to that of 5 nM glucagon, these two agents induced a more prolonged elevation of [Ca2+]c. Glucagon-induced elevation of [Ca2+]c was accompanied by a smaller increase in cyclic AMP than that induced by forskolin. When the cyclic AMP response to glucagon was potentiated by an inhibitor of phosphodiesterase, 3-isobutyl-1-methylxanthine, the glucagon-induced increase in [Ca2+]c was not affected. Conversely, when the cyclic AMP response to glucagon was reduced by pretreatment of the cells with angiotensin II, glucagon-induced changes in [Ca2+]c were rather enhanced. Furthermore, **vasopressin** potentiated glucagon-induced changes in [Ca2+]c despite the reduction of the cyclic AMP response to glucagon. In the presence of 1 microM extracellular calcium, angiotensin II did not enhance glucagon-induced changes in [Ca2+]c. These results suggest that at least part of the action of 5 nM glucagon on calcium mobilization is independent of cyclic AMP.

L23 ANSWER 18 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

1987:140101 Document No.: PREV198732068736; BR32:68736. ANGIOTENSIN II AII AND

VASOPRESSIN AVP STIMULATE CALCIUM-ACTIVATED CHLORIDE CONDUCTANCE IN CULTURED RAT MESANGIAL CELLS BY RELEASING CALCIUM FROM INTRACELLULAR ORGANELLAE. OKUDA T [Reprint author]; YAMASHITA N; KOJIMA I; **OGATA E**; KUROKAWA K. IVTH INT MED, UNIV TOKYO SCH MED, TOKYO, JPN. Kidney International, (1987) Vol. 31, No. 1, pp. 282.
Meeting Info.: MEETING OF THE AMERICAN SOCIETY OF NEPHROLOGY, WASHINGTON, D.C., USA, DECEMBER 7-10, 1986. KIDNEY INT.
CODEN: KDYIA5. ISSN: 0085-2538. Language: ENGLISH.

L23 ANSWER 19 OF 23 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
1987:17089 The Genuine Article (R) Number: F4838. ANGIOTENSIN-II (AII) AND **VASOPRESSIN** (AVP) STIMULATE CA++-ACTIVATED C1-CONDUCTANCE IN CULTURED RAT MESANGIAL CELLS BY RELEASING CA++ FROM INTRACELLULAR ORGANELLAE. OKUDA T (Reprint); YAMASHITA N; KOJIMA I; **OGATA E**; KUROKAWA K. UNIV TOKYO, SCH MED, DEPT INTERNAL MED 14, TOKYO 113, JAPAN. KIDNEY INTERNATIONAL (JAN 1987) Vol. 31, No. 1, pp. 282-282. ISSN: 0085-2538. Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148. Language: English.

L23 ANSWER 20 OF 23 MEDLINE on STN DUPLICATE 7
86323276. PubMed ID: 3092832. Evidence for direct effect of tolbutamide on hepatic glycogenolysis induced by Ca2+-dependent hormones. Mine T; Kimura S; Ohsawa H; **Ogata E.** Biochemical pharmacology, (1986 Sep 15) 35 (18) 3103-7. Journal code: 0101032. ISSN: 0006-2952. Pub. country: ENGLAND: United Kingdom. Language: English.
AB The effects of tolbutamide and glibenclamide on hepatic glycogenolysis in perfused rat liver were investigated. Tolbutamide per se did not influence glucose output from the liver, but at therapeutic concentrations (about 350 microM) it significantly inhibited the glycogenolysis induced by phenylephrine, **vasopressin** and angiotensin II, while glibenclamide did not. Neither tolbutamide nor glibenclamide inhibited the glycogenolysis induced by glucagon. Tolbutamide potentiated the inhibitory effect of submaximal concentrations of insulin on glycogenolysis induced by phenylephrine. This effect of tolbutamide was elicitable even in the absence of calcium in the perfusate, and was additive to that of trifluoperazine. However, tolbutamide did not potentiate the inhibitory effect of insulin on glucagon-induced glycogenolysis. Tolbutamide inhibited the glycogenolysis induced by A23187, a calcium ionophore. These results indicate that, in addition to its known effect on insulin secretion, tolbutamide has a direct effect on the liver to inhibit glycogenolysis induced by Ca2+-dependent hormones (catecholamines, **vasopressin** and angiotensin II) and A23187. Thus, it is likely that tolbutamide inhibits the effect of Ca2+ mobilized by Ca2+-dependent hormones to stimulate glycogenolysis.

L23 ANSWER 21 OF 23 MEDLINE on STN DUPLICATE 8
87048732. PubMed ID: 3778438. Comparison of the changes in cytoplasmic free calcium concentration induced by phenylephrine, **vasopressin** and angiotensin II in hepatocytes. Mine T; Kojima I; Kimura S; **Ogata E.** Biochemical and biophysical research communications, (1986 Oct 15) 140 (1) 107-13. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.
AB Effects of phenylephrine, **vasopressin** and angiotensin II on cytoplasmic free calcium concentration, [Ca2+]c, were examined by monitoring aequorin bioluminescence in isolated hepatocytes preloaded with aequorin. In the presence of 0.5 mM calcium in the medium, the pattern of changes in aequorin bioluminescence induced by phenylephrine was different from that induced by **vasopressin** or angiotensin II. When extracellular calcium concentration was reduced to 1 microM, however, these three agents induced identical changes in aequorin bioluminescence. These results suggest that the mode of action of phenylephrine on cytoplasmic free calcium concentration differs from that of either **vasopressin** or angiotensin II and that the difference in ability to increase calcium influx may account for the distinct patterns induced

by these agents.

L23 ANSWER 22 OF 23 MEDLINE on STN DUPLICATE 9
86006657. PubMed ID: 3899890. Influence of extracellular phosphate concentrations on the regulation of hepatic glucose output. Mine T; Kimura S; Koide Y; Ohsawa H; **Ogata E.** Hormone and metabolic research. Hormon- und Stoffwechselforschung. Hormones et metabolisme, (1985 Sep) 17 (9) 438-42. Journal code: 0177722. ISSN: 0018-5043. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB Experiments were carried out to investigate the role of extracellular phosphate in the hormonal regulation of glycogenolysis in perfused fed-rat liver. Omission of phosphate from the perfusate did not affect the ATP, ADP and AMP contents of the tissue and the basal glucose output from the perfused liver. However, it inhibited significantly the glycogenolysis induced by glucagon, cyclic AMP, phenylephrine and **vasopressin** but not that induced by 2,4-dinitrophenol. In the absence of perfusate phosphate, the increase in phosphorylase a activity caused by the addition of glucagon, phenylephrine and **vasopressin** was significantly less than that observed in the presence of perfusate phosphate. Insulin inhibition of the glucagon- or cyclic AMP-induced glycogenolysis was abolished when the perfusion was carried out with the phosphate-free buffer. However, the inhibitory effect of insulin on phenylephrine-induced glycogenolysis was clearly demonstrated even when the perfusate contained no phosphate. These data indicate that in the phosphate-depleted liver, the hormonal control of phosphorylation and dephosphorylation of phosphorylase is impaired. The difference in the phosphate dependency of insulin action on glucagon-and alpha-adrenergic agonist-induced glycogenolysis suggests that the mechanism or site of insulin action on glucagon and phenylephrine is different.

L23 ANSWER 23 OF 23 MEDLINE on STN DUPLICATE 10
83211579. PubMed ID: 6303930. Inhibitory effect of [Asu1 . 7]-eel calcitonin on glucagon-induced glycogenolysis in perfused rat liver. Mine T; Kimura S; **Ogata E.** Hormone and metabolic research. Hormon- und Stoffwechselforschung. Hormones et metabolisme, (1983 Mar) 15 (3) 139-43. Journal code: 0177722. ISSN: 0018-5043. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB In an attempt to elucidate the mechanism by which calcitonin modulates glucose metabolism, the effect of elcatonin ([Asu1 . 7]-eel calcitonin), a potent synthetic eel calcitonin analogue, on hepatic glycogenolysis was investigated by use of perfused liver from fed rats. Elcatonin, as infused into the portal vein at concentrations between 10 mU/ml and 200 mU/ml did not affect glucose output into the hepatic venous effluent. At concentrations higher than 100 mU/ml, it inhibited the glycogenolysis stimulated by submaximal concentrations of glucagon which was perfused concurrently. This aspect of elcatonin effect was reproduced by synthetic salmon calcitonin. Though elcatonin showed a marked inhibition of the glycogenolytic activity induced by glucagon at or less than 5.7 X 10(-11) M, the inhibitory effect became undetectable when higher concentrations of glucagon were employed. Elcatonin did not inhibit the glycogenolysis induced by dibutyryl cyclic AMP at near (0.5 microM) or less than half-maximally effective (0.2 microM) concentrations. In addition, it did not inhibit the glycogenolytic activity half-maximally stimulated by alpha-adrenergic agonist (phenylephrine, 0.4 microM) or **vasopressin** (0.2 mU/ml). Elcatonin inhibited the cyclic AMP production of the tissue induced by glucagon infusion. These data indicate that elcatonin modulates hepatic glycogenolysis by preventing the glucagon effect at a step before cyclic AMP production and with an apparently competitive kinetics. In view of the concept that Ca++ is involved in the glycogenolytic effect of alpha-adrenergic agonist and **vasopressin**, the fact that elcatonin did not influence the action of these agents suggests that Ca++ fluxes are not involved in the elcatonin effect on liver.